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RETINAL APLASIA AS A CLINICAL ENTITY

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[WITH SPECIAL PLATE]

Blindness in infants is occasionally seen with apparently normal eyes or eyes in which minimal fundus anomalies are present. Such cases present considerable diagnostic difficulties. Frequently there is uncertainty whether the disks are normal or atrophic, and the term "cortical blindness" is occasionally used, though this is little more than a terminological escape from a real problem. When fundus anomalies are present they are generally ill defined and have an uncharacteristic appearance, such as the occasional diffuse fine pigmentation that goes under the designation of "pepper-and-salt fundus"—a fairly definite recognition that there is some form of retinal atrophy. The after-history of these cases with apparently normal fundi or fundi with minimal anomalies is not well established. The following case reports are presented as indicating that some of these cases, at any rate, are genetic in origin and progressive in character.

Case Reports

1. The M–n Family

Pedigree Chart 1 shows five observed cases of blindness over two generations, with a probable sixth case in an antecedent generation. None of the marriages recorded were consanguineous.

Case 1.—Gerald M., the proband (III, 16 in Chart 1), aged 9 years. Blindness was noted in infancy, and the child was admitted to the Ellen Terry Home at Reigate at the age of 6 as blind and mentally defective. The general appearance of the boy is normal. His head is small, but within normal limits. Apart from mental defect there is no gross abnormality of his central nervous system. At the age of 8 he had a developmental age of about 2½ years. There is no evidence of any environmental factor which might have caused the mental defect. The eyes are outwardly normal. The fundi (Special Plate, Fig. 1) show diffuse and rather gross pepper-and-salt pigmentation, exposure of the choroidal pattern, narrow retinal arteries, and uniformly grey disks, the margins of which are not sharply defined. The pupils react sluggishly to light, but the child does not seem to possess any perception of light. The most incongruous aspect is the disproportion between the relatively slight ophthalmoscopic findings and the gross visual defect.

Case 2.—Ronald M. (III, 13); aged 15 years, eldest brother of the proband. Blindness was noted at 6 weeks, and he was grossly backward from infancy. He was admitted to the Ellen Terry Home, Reigate, at the age of 6 years. Apart from his idiocy he had no other signs of neurological disorder. He was later transferred to Pewsey Hospital, where he died at the age of 15. When examined three months before his death both eyes appeared sunken in. There was severe nystagmus, and apparently no perception of light, as the pupils were inactive. The media were clear. The fundi showed pale atrophic disks with thin vessels, and scattered all over the fundus background were areas of pigmentation and atrophy of the diffuse chorio-retinitis type. Fairly large transverse oval atrophic patches were present towards the central area, placed symmetrically in the two eyes. The retinal appearances were therefore of essentially the same order as those shown by his brother, though at a more advanced stage. Post mortem the brain

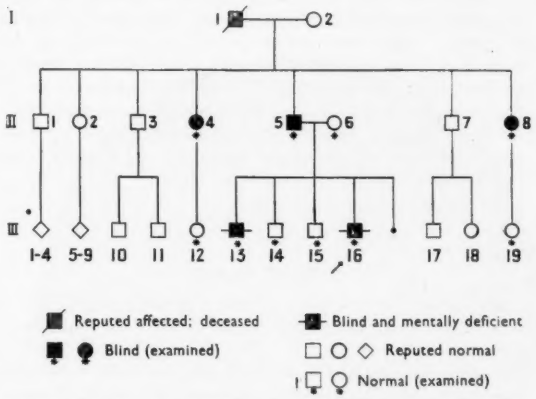

CHART 1.—The M–n family. The proband is indicated by an arrow.

showed no gross abnormalities (Dr. L. Crome and Dr. D. Oppenheimer), while the retina showed extensive atrophy involving all the layers.

Case 3.—William M. (II, 5), aged 38, the father of Cases 1 and 2; he is an alert, intelligent man, and has been blind from birth. The eyes are outwardly normal. He has no perception of light and never has had any. Nystagmus of the pendulum type is present. Ophthalmoscopically, the appearances are those seen in his eldest son, though markedly exaggerated. The normal landmarks in the fundi are not readily picked up; the background is not uniform in colour: in the central area it is rather atrophic with a tendency for the underlying sclerotic to show through; elsewhere there is a diffuse whitish sheen broken by much

crude pigment irregularly scattered over the fundi and definitely not of the bone-corpuscle type. The disk itself is ill defined in the surrounding atrophic retina, and the vessels are markedly narrowed. A striking feature is the essential symmetry in appearance of the two fundi.

Case 4.—Mrs. Daisy L. (II, 8), aged 30, an aunt of the affected children. She too is mentally normal, and has been blind from birth. She has no perception of light and never has had any. Nystagmus is present. Her fundi are very similar in detail to those of her eldest nephew.

Case 5.—Mrs. Dorothy M–k (II, 4), aged 40, another aunt of the affected children. Like her brother and sister, she has been totally blind since birth, never having possessed any perception of light. The eyes are outwardly normal apart from nystagmus, and she is mentally normal. Ophthalmoscopically, the appearances are more complicated than in the other members of the family. The right eye shows lenticonus posterior, while the fundus (Special Plate, Fig. 2) shows a uniformly white disk with the vessels barely perceptible. In the background there are many localized atrophic areas with irregular edges, too jagged to fit into the picture of gyrate atrophy. In the left eye the lens is dislocated into the vitreous and the fundus is most unusual. There is little red reflex, most of the retina being detached and dirty grey in appearance, suggestive of much fibrosis. Such red reflex as is present is broken by exceptionally heavy pigmentation. The disk is markedly white and the vessels are exceedingly attenuated. There is no history of trauma.

Excluding the appearance in the left eye in Case 5, as probably complicated by secondary effects of trauma, these five cases show a progressive increase of fundus lesions with age, the mildest being of the proband. It is likely that the trouble originated with I, 1, who died at the age of 53, but had been blind from birth. According to the history given by his son, II, 5, the trouble had been diagnosed as disease of the optic nerve; he is reported to have been mentally normal.

These five cases have in common a history of total blindness going back to infancy, and presumably present at birth. The basic lesion in all five is likely to be retinal in site and progressive in character—a reading supported by the presence of severe nystagmus even in the youngest patient. It is particularly noteworthy that in the youngest patients the ophthalmoscopic appearances are relatively mild and unspecific, as distinct from the heavy involvement seen later in life. The mode of inheritance is clearly dominant.

2. The R–e Family

Pedigree Chart 2 shows four affected children in a sibship of five, the offspring of unaffected and non-consanguineous parents. The four affected children were first seen by one of us (A. S.) in 1949, and presented essentially identical fundus appearances: optic atrophy with some narrowing of the retinal vessels in addition to considerable mottling of the maculae, without any obvious involvement of the rest of the fundus. As there were no neurological associations, and the eldest of the four affected children was 9 years of age and the youngest 1 year old, and as all the children had been affected from early infancy, it was clear that a cerebro-macular affection of either infantile or juvenile type was excluded, while the optic atrophy, as also the age distribution, excluded the possibility of macular dystrophy. No further investigation could be carried out at the time.

This family came recently under the supervision of one of us (C. W.), and thus offered the opportunity of further examination. The clinical details of these four patients were as follows:

Case 6.—Grace R. (II, 1 in Chart 2), aged 19. Labour was prolonged and difficult; weight at birth was 5½ lb. (2.495 kg.). The child's face was said to have been severely bruised. Blindness was noted in infancy, and appears to have presented considerable diagnostic difficulties. Different observers, judging by the documentary evidence, had regarded the fundus appearances as those of optic atrophy, retinal atrophy, macular degeneration, and malformation of the optic disk. She was slow in attaining the normal milestones of development, and was deemed to be educationally subnormal. Physically she is rather dwarfed. There is no

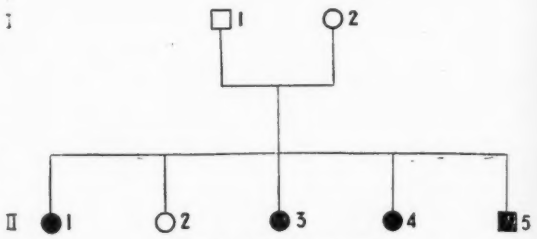

CHART 2.—The R–e family.

evidence of neurological disorder. In regard to both her physique and her intelligence level she differs from her other four siblings, who are within the normal range. Emotionally she is very immature, and she is in need of special care, being incapable of supporting herself or of managing her affairs without a good deal of help.

When she was re-examined recently the findings in the right eye were those shown in Special Plate, Fig. 3. The disk was atrophic; the retinal vessels were attenuated; there was mottling at the macula, while the periphery showed some sheen with fine pepper-and-salt mottling. The picture was therefore one of retinal atrophy. The lens showed a small posterior cortical opacity. In the left eye the iris was atrophic and the lens totally opaque. There was no perception of light in either eye, and the eyes showed rather marked pendulum nystagmus.

Case 7.—Jennifer R. (II, 3), aged 15. The blindness was noted in infancy. Mentally she is normal. Perception of light was present in the left eye, but only doubtfully present in the right, while both eyes showed pendulum nystagmus. The fundi were essentially similar to those of her elder sister—atrophic disks, marked attenuation of the vessels, and an ill-defined granular appearance over the whole of the fundus. The left macula was ill defined, but the right showed a pigmented scar very much like a coloboma.

Case 8.—Margaret R. (II, 4), aged 12. Here too blindness was noted in infancy, and intelligence is normal. Nystagmus was present, while perception of light was absent. The appearances of the disk and vessels were those seen in her sisters, but the fundus background was distinctly more patterned, as can be seen from Special Plate, Fig. 4. There were areas of depigmentation throughout, with exposure of the choroidal vessels here and there, and possibly hyaline dots towards the centre.

Case 9.—Edward R. (II, 5), aged 11. The history here, and the mental condition, are as in Cases 7 and 8. He has no perception of light. Nystagmus is more marked than in his sisters, while the disk and vessels are very similar. The maculae could not be defined; the fundus background showed in a mild form the same type of depigmentation as seen in his sister Margaret.

In this family the affection was in all probability present since birth, and showed the total blindness seen in the first family. The two youngest members showed a rather more advanced fundus picture than the two

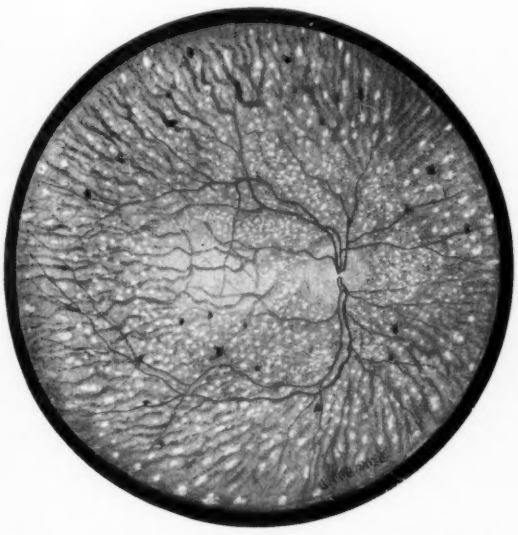

FIG. 1.—The right fundus in Case 1, a boy aged 9. The disk is grey, the arteries and veins are narrow, and the fundus background shows diffuse mottling of a crude pepper-and-salt type.

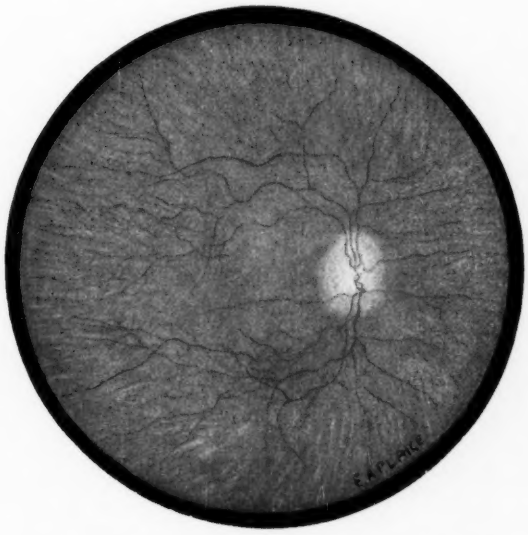

FIG. 3.—The right fundus in Case 6, a girl aged 19. There is marked optic atrophy, with fine pepper-and-salt changes throughout the fundus.

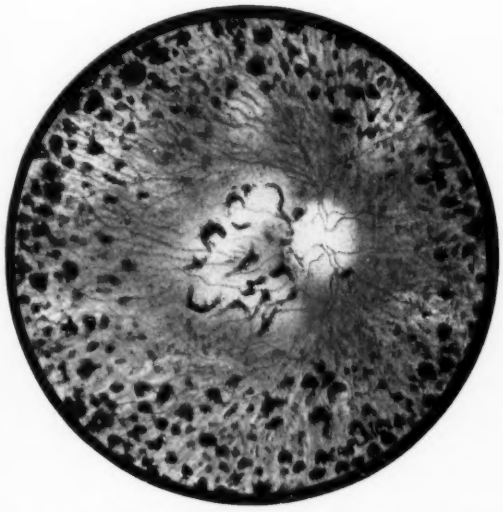

FIG. 2.—The right fundus in Case 5, a woman aged 40, an aunt of the boy shown in Fig. 1. In addition to advanced optic atrophy with marked narrowing of the retinal vessels, there is crude pigmentation scattered throughout the fundus with extensive areas of chorio-retinal atrophy.

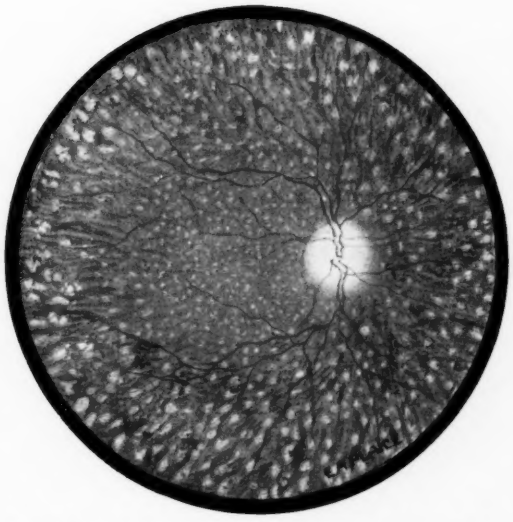

FIG. 4.—The right fundus in Case 8, a younger sister of the patient shown in Fig. 3. The fundus background shows the same advanced optic atrophy, and a considerably more obvious retinal atrophy is shown by the crude pepper-and-salt patterning. Note the similarity to Fig. 1 depicting a member of a different family.

oldest children, but in all four the pattern was clearly that of an extensive retinal atrophy involving the maculae and disks. Mentally the children were normal, except that the eldest was rather simple. In all probability the mode of inheritance was recessive.

Discussion

1. Retinal Aplasia as a Clinical Entity

The two families recorded here have in common total or subtotal blindness present in infancy, and probably from birth, with a presumably featureless fundus other than an ill-defined macular area and pale disks; nystagmus may possibly be present from the beginning. Cases of this type are not particularly uncommon as isolated occurrences, and the difficulty in diagnosis they present has already been indicated. The present study brings out the fact that not only are some at least of these cases genetic in origin, but that the affection can be either recessive or dominant.

The evidence for a recessive affection is broadly based, for the recent study by Alström and Olson (1957) has clearly defined this entity. Since 1897 elementary education has been compulsory for blind children in Sweden, and there is one central elementary school through which they all have to pass. In an investigation on the material from 1897 to 1948 they paid special attention to the cases recorded as congenital retino-choroiditis without known cause. It became clear that these cases were proband material leading to families, and altogether 105 families were isolated. The material was found to overlap with cases admitted as suffering from "congenital amaurosis" and from congenital optic atrophy of unknown origin. In all, 175 affected and 303 unaffected sibs were traced. Cases examined under the age of 15 years were found to consist of 61% with "retino-choroiditis," 28% with congenital amblyopia, and 10% with optic atrophy. Two cases had cataract on admission to the school. When the collected material was classified into three age-groups—under 15, 15–45 years of age, and over 45—the incidence and extent of retino-choroidal changes were found to increase progressively, while the incidence of congenital amblyopia without fundus lesions declined. The term "retino-choroidal changes" covers a wide range of lesions from minute round pale spots at the periphery, scarcely visible, to heavy irregular pigmentation scattered throughout the fundus. While some optic atrophy and a moderate degree of narrowing of the vessels were common, optic-nerve lesions were not as conspicuous as in cases of retinitis pigmentosa with equally severe impairment of sight. Moreover, in the youngest age-group total or subtotal blindness without any fundus changes was present in some 33% of cases. Associated conditions were cataract and keratoconus—cataract being present in some 10% of the youngest patients and increasingly in the higher age-groups, while keratoconus was present only exceptionally in young patients, but again increased with age. Different members of the same sibship showed the different components to a variable degree. Variations therefore occur not only with age, but as between families and between individuals within the same family. A striking aspect was the gross impairment of vision noted soon after birth or during the first year of life. Nystagmus was a common association, and the electroretinographic response was abolished in almost all cases. Genetic analysis showed the condition to be a monofactorial recessive affection widely scattered throughout Sweden, with a probable mutation rate of $2.3–10^{-5}$. There was no significant excess of mental anomalies in this group. Alström and Olson regard the affection as responsible for about 10% of all cases of blindness in Sweden.

A recent investigation into the causes of blindness in the Netherlands revealed 227 cases of this affection—114 in adults and 113 in children (Schappert-Kimmijser *et al.*, 1959). These observers estimated that 18% of all blind children in Holland suffer from this affection. Of 56 children examined in detail, 14 showed major neurological or psychiatric disturbances, including 5 cases of epilepsy. The affection was recessive and particularly prevalent on the isolated outlying island of Urk, where consanguineous marriages had been common for several centuries.

The findings recorded in the second family in the present study clearly conform to the accounts given by the Swedish and the Dutch observers, down to the detail that in this one family there were variations in the fundus appearances, a mental anomaly, and lens changes.

The occurrence of the same affection as a dominant disturbance is suggested by the report on the first family. The fundus appearances and the clinical course in the two families are so similar that it would be impossible to distinguish—except by the family history—a member of the first family with its dominant inheritance from a member of a family with the recessive type. Alström and Olson have suggested the name of "heredo-retinopathia congenitalis monohybrida recessiva autosomalis." It is obviously not advisable to label the affection as exclusively recessive. Even the designation of "heredo-retinopathia congenitalis" is not very happy, nor is the designation "amaurosis congenita (Leber)" suggested by Schappert-Kimmijser *et al.* The simpler term "retinal maldevelopment" or "retinal aplasia" would serve as well.

2. The Wide Range of Fundus Appearances in Retinal Aplasia

The marked polymorphism of the fundus lesion is clearly seen when comparing the early stages with the end stages. Progressive changes do, of course, occur with all abiotrophies, but generally, as in retinitis pigmentosa, the different stages are clearly recognizable as belonging to the same affection. Retinal aplasia falls within the small group of disorders in which the wide range of appearances during the course of the affection are such that they are not readily recognized as belonging to the same disorder. While this makes diagnosis more complex, it helps in recognizing the significance of unusual fundus appearances. Retinal aplasia is in this respect as protean as choroideremia and generalized fundus dystrophy with their exceptionally wide range of intermediate stages.

3. The Mental Defect

In contrast to the relatively mild mental anomaly in one patient in the second family, the first family showed severe mental deficiency of a non-specific type in the two affected children in the third generation, though the three affected members in the second generation were mentally normal, and the reputedly affected individual in the first generation was presumably also normal. As there was no gross structural defect in the brain of Case 2, as seen post mortem, and the brain is at present being studied in greater detail, it is best to

leave this aspect for future consideration. It is not possible on the available evidence to decide whether a severe mental defect is indeed an inconstant component of the dominant variety of the affection.

4. Differential Diagnosis

Once it is appreciated that retinal aplasia is a congenital anomaly with a progressive course, there is little to take into account in the differential diagnosis of the affection. The following considerations arise.

Congenital Hereditary Optic Atrophy.—It is likely that in some families congenital optic atrophy runs such a severe course that there is blindness from birth. Commonly, however, congenital optic atrophy shows deep atrophic cupping, and there is a relatively mild disturbance of vision with relatively slow progression of the defect. The total or subtotal blindness seen in retinal aplasia is therefore the significant point in the differential diagnosis of the two affections. Thus the progressive course of congenital hereditary optic atrophy is shown by increasing failure of vision, whereas the progressive character of retinal aplasia is revealed not so much by the increase of the blindness—which in most cases is total to begin with—but by the increasing pigmentary and atrophic changes in the retina. The modes of inheritance of the two affections do not help very much, for both apparently have recessive and dominant forms. For the present little is known of the relative frequency of the dominant and recessive types in either of these affections.

Congenital Optic Atrophy of Uncertain Origin.—When an environmental factor cannot be clearly established in a sporadic case of optic atrophy present at birth, the possibility that the infant represents an isolated case of hereditary optic atrophy or of retinal aplasia must be considered. Without the supporting evidence of other cases in the family the diagnosis will remain uncertain until the secondary degenerative changes of the retina in retinal aplasia become manifest later in life.

Aplasia of the Optic Disk.—Here the obvious anomaly of the disk, and possibly also vascular anomalies, are pathognomonic.

Chorio-retinitis of Inflammatory or Infective Origin.—In their early stages the ophthalmoscopic features in the retinitis resulting from maternal rubella during pregnancy, and in the lesions of congenital syphilis, congenital toxoplasmosis, and congenital cytomegalic inclusion disease, are all likely to be considerable, while the visual defect is unlike the total or subtotal blindness seen in retinal aplasia. In the later stages, with possibly increasing visual disability, the history would indicate that the inflammatory disorders began with relatively mild visual disturbances.

Cerebro-macular Degeneration.—The characteristic age of onset and clinical course and the associated neurological disturbances of the different clinical types of cerebro-macular degeneration preclude any difficulties in the differential diagnosis.

Retinitis Pigmentosa and the Macular Dystrophies.—These conditions hardly arise in the differential diagnosis, as the affected children were normal ophthalmoscopically and had normal visual acuity until the onset of the affection at variable periods in life—a sharp contrast to the blindness at birth in retinal aplasia.

5. Possible Pathological Basis

The one histological examination at hand refers to the retina in a boy aged 16, and, as already noted, there was a non-characteristic extensive degeneration of all the layers. Until histological material of a retina at a very much earlier stage becomes available it is impossible to incriminate specifically the neuro-epithelium or any other layer; one can only offer surmises of a general character. The intensity of the lesion at birth presupposes that the retina either had failed to develop into functioning layers or had developed normally only to degenerate before birth. It is tempting to draw a parallel with retinitis pigmentosa. We now know that in retinal dystrophy in the mouse, the Irish setter, and the rat, where the ophthalmoscopic picture and clinical course are reminiscent of human retinitis pigmentosa, the affection is due to failure in the final differentiation in the rod layer, which itself is already laid down and clearly distinguishable (Sorsby *et al.*, 1954; Lucas, 1954; and Lucas *et al.*, 1955). If human retinitis pigmentosa does indeed represent a retina that has developed fully enough to function apparently normally—though presumably not so fully as to give a normal electroretinographic response or normal dark-adaptation—then retinal aplasia might be considered as the counterpart of retinitis pigmentosa in so far as the failure of development has occurred at an earlier stage, so that the retina has never reached functional maturity. On this reading retinal aplasia and retinitis pigmentosa are in fact closely allied affections, aplasia representing an earlier and more severe failure in retinal development. Both affections have a considerable post-natal course. In retinal aplasia this is shown by degenerative changes visible ophthalmoscopically, and presumably histologically; in retinitis pigmentosa the post-natal changes are shown by the development of the typical ophthalmoscopic picture and the steady disintegration of visual functions.

6. The Place of Aplasia Among Congenital Anomalies

Blindness at birth is not a common affection, and when present there are generally obvious physical anomalies in the globe, extending up to anophthalmos. These are the classical congenital defects. Retinal aplasia is of significance in that, like retinitis pigmentosa, it focuses attention on the failure of development affecting not the eye as a whole but a particular tissue. For the present it is enough to raise the possibility that ocular tissues may show developmental arrest at different stages of development (including post-natal development) without necessarily showing the classical features of a congenital defect. In this scheme a congenital defect would represent an anomaly involving the whole organ, aplasia an arrested development of a tissue—an arrest sufficiently severe to prevent normal function—and dystrophy a post-natal degeneration of a tissue that has developed sufficiently to function adequately till degenerative changes set in.

Summary

An account is given of two family groups in which blindness was present early in infancy and in all probability from birth. The eyes are normally formed and the media clear; ophthalmoscopically the initial findings are of either a normal or slightly pale disk, and some mottling of the fundus background. While the blindness is generally total from the beginning, the

ophthalmoscopic features progress throughout life, giving crude pigmentary reactions of the chorio-retinitis type and well-established optic atrophy.

In one family the mode of inheritance was clearly dominant; in the second family it was in all probability recessive. In the first family the two affected children in the third generation showed gross mental defect. In the second family only one of the four affected sibs showed a mental anomaly, and that slight.

The brain and the eyes of the older of the two children in the first family came to necropsy. The brain showed no gross macroscopic anomalies; the retina was disorganized beyond the possibility of recognizing individual layers. The brain is being subjected to a more detailed study.

It is suggested that the blindness recorded here is determined by a failure of the retina to develop into a functioning tissue—aplasia of the retina—and that this undeveloped retina subsequently undergoes secondary degenerative changes. Attention is drawn to a possible parallel with the changes in the more fully developed retina seen in retinal dystrophy—a genetically determined retinal degeneration—in some strains of mice, rats, and the Irish setter.

It is pointed out that the findings in the second family recorded here conform to those described by Alström and Olson in their study on 105 families in Sweden in whom they observed a recessively inherited congenital retinopathy, and to the cases more recently reported from Holland.

We are indebted to Dr. L. T. Hilliard, of the Fountain Hospital, Dr. A. E. P. Swinson and Dr. S. L. Pugmire, of Pewsey Hospital, Swindon, the Rev. B. G. Bartlett and Miss E. A. Cronin, of the Royal School for the Blind, Leatherhead, and Mr. R. Peppitt, of Linden Lodge School, for facilities to carry through the investigations recorded. We are obliged to Dr. D. Oppenheimer, of the Radcliffe Infirmary, Oxford, and Dr. L. Crome, of the Fountain Hospital, for pathological material and information.

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The "Recommendation on the Organization of Occupational Health Services in Places of Employment," discussed at the International Labour Conference in 1959, enumerates the functions of such services, having first stated that their role is essentially preventive. The list of functions includes surveillance within the undertaking of all factors which may affect the health of workers, and advice in this respect to management and to workers or their representatives in the undertaking; pre-employment, periodical, and special medical examinations; training of first-aid personnel and supervision and maintenance of first-aid equipment; education of works personnel in health and hygiene; compilation and periodic review of relevant statistics and research in occupational health. The United Kingdom Government and employers' and workers' delegates all voted in favour of this recommendation. A subject discussed for the first time with a view to the adoption of international regulations at the 1960 conference was protection of workers against ionizing radiation. (*International Labour Conference, 43rd Session, Geneva, 1959*, H.M.S.O., price 35s. 6d.)

CHEMOTHERAPY IN CHRONIC BRONCHITIS

INFLUENCE OF DAILY PENICILLIN AND TETRACYCLINE ON EXACERBATIONS AND THEIR COST

A REPORT TO THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION BY THEIR CHRONIC BRONCHITIS SUBCOMMITTEE*

PREPARED BY

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Between June, 1955, and June, 1956, bronchitis caused the loss of 22 million working days among men in England and Wales, representing about a quarter of all male sickness incapacity (Ministry of Pensions and National Insurance).

Previous work has suggested that antibiotic treatment is of value in this condition; much of this work has been reviewed by May (1958), who considered the tetracycline group of compounds to be the most satisfactory. These compounds were used in recent investigations by Edwards *et al.* (1957), Elmes *et al.* (1957), Buchanan *et al.* (1958), and Moyes and Kalinowski (1959). Antibiotics may be given continuously throughout the winter on a prophylactic basis, or for short periods at the onset of certain respiratory symptoms, there being no clear evidence that either method is preferable. It has been suggested, however (May, 1958; Moyes and Kalinowski, 1959), that, where the expected number of attacks is small, intermittent treatment is less costly, the converse being true for more severe cases likely to have frequent attacks. The prophylactic value of 1 g. daily of potassium penicillin G and 2 g. daily of tetracycline were compared in a study by Cherniack *et al.* (1959). Penicillin was found ineffective compared with tetracycline in this trial, but 45 out of the 67 patients had demonstrable bronchiectasis, and the duration of treatment varied from 3 to 18 months, the seasonal differences being unstated. The diagnoses of patients lost from study were not stated, and on the whole the findings cannot be taken as applying to patients suffering from bronchitis.

The present trial† was undertaken first because previous trials had been based on small numbers and confirmatory evidence seemed desirable; secondly, the high cost of the tetracycline compounds suggested that the value of

*Members of the Subcommittee are: Dr. P. Baldry, Dr. J. R. Bignall, Dr. R. S. Francis, Dr. S. W. A. Kuper, Dr. G. P. Maher-Loughnan (honorary secretary), Dr. Robert May, Dr. E. N. Moyes, Dr. P. D. Oldham, Dr. Hugh Ramsay (chairman), and Dr. C. C. Spicer.

Dr. R. S. Francis and Dr. C. C. Spicer co-ordinated the work and prepared the report, which should be referred to as "British Tuberculosis Association (1959) . . . etc."

†The investigation was carried out at the following centres: Cambridge chest clinic (Dr. M. J. Greenberg and Dr. R. Bruce). Chertsey chest clinic (Dr. N. V. Birrell). Croydon chest clinic (Dr. R. J. H. Fanthorpe and Dr. J. F. Heffernan). Dudley chest clinic (Dr. M. Sheldon). Dundee chest clinic (Dr. R. N. Johnston). Edmonton chest clinic (Dr. R. S. Francis). Finchley chest clinic (Dr. B. A. Butterworth). Ipswich chest clinic (Dr. P. Embleton and Dr. D. van Zwanenberg). Islington chest clinic (Dr. J. Wallace Craig). Mansfield chest clinic (Dr. D. Davis). Preston chest clinic (Dr. M. R. Geake and Dr. R. S. Nicholson). Reading chest clinic (Dr. A. J. Karlish). St. Albans chest clinic (Dr. T. A. Watkin Edwards). Tunbridge Wells chest clinic (Dr. R. May). Walthamstow chest clinic (Dr. H. Ramsay). Willesden chest clinic (Dr. C. H. C. Toussaint and Dr. J. Mikhail).

penicillin should be tested as a possible alternative, since Douglas *et al.* (1957) reported favourably on this drug in infective exacerbations of chronic bronchitis with purulent sputum. Finally, a special study seemed to be required, relating the cost of treatment to the money lost by incapacity.

Material and Methods

Central Organization

The principle of daily prophylactic treatment was adopted. Sixteen chest-clinic physicians co-operated in a double-blind controlled trial, contributing 252 patients who were allotted at random to three groups receiving: (1) tetracycline, 250 mg. b.d. in capsules; (2) penicillin V (as potassium salt), 312 mg. b.d. in capsules—equivalent to 1 million units daily; (3) inert (starch) capsules b.d.

All capsules were identical in appearance, and it was arranged that all patients should start treatment on January 5, and cease on April 30, 1959. Information was to be recorded as to the number and duration of "bronchitic exacerbations and pneumonic episodes" in each group of cases, the average number of working days lost as a result, and the money lost to the patient through time off work and to the State from sickness benefit. The term "pneumonic episode" was not specifically defined, but in order to concentrate on the type of attack most likely to be improved by antibiotics the following definition of "bronchitic exacerbation" was adopted: "An increase in cough with the appearance of pus in the sputum or an increase in the amount of pus over the amount usually present."

By special arrangement the following data were obtained from the Ministry of Pensions and National Insurance concerning each patient's claims for sickness benefit in consequence of "bronchitis" or pneumonia of any kind: (1) the number of years during the past decade in which such a claim was made; and (2) the total number of spells, and their duration, for which such claims were made, since January, 1955.

The purpose of this and certain other information was to check the randomization procedure. Later, as a final check on the results of the trial, details of all the patients' claims for respiratory disease, other than tuberculosis and neoplasm during the period of the trial, were obtained from the Ministry.

A full survey of sputum bacteriology was not considered practicable, but nasal swabs, taken before and after the trial, were cultured at local laboratories and coagulase-positive staphylococci were forwarded to Dr. Robert May at Brompton Hospital, for sensitivity tests (see Appendix II).

Chest Clinic Organization

Each clinic physician recruited up to 20 patients fulfilling the following criteria (see Elmes *et al.*, 1957): They must be wage-earning males aged 30–65 who have suffered from winter cough with sputum for the past three years, during which time they must have been off work twice because of bronchitis with purulent sputum. They must be reasonably intelligent and be prepared to co-operate even if treatment appears unhelpful. Patients were not accepted if their main symptom was wheezing, if their history included heart failure or penicillin sensitivity, if there were radiographic changes other than those of bronchitis and emphysema, or if they were already taking part in a trial of chemotherapy or vaccine to reduce the incidence of bronchitis.

The co-operation of the general practitioners was sought, and they remained in sole clinical charge of the patients during any episodes of ill-health, being free to prescribe whatever treatment they wished. They were asked, however, not to give any other prophylactic chemotherapy, and to inform the chest clinic of drug reactions, pneumonic episodes, and any chemotherapy prescribed as a result of illness. They were also asked not to advise patients to omit the capsules supplied from the clinic, unless toxic symptoms occurred.

Within each clinic, chest physician, health visitors, and almoner worked as a team. At the pre-trial interview each patient was carefully instructed. He was given a graduated sputum flask and a diary in which to make the following records:

1. 24-hour sputum volume once weekly, and daily when off sick with bronchitis or pneumonia.

2. Daily sputum colour, and whether the same, more, or less sputum than usual (approximately).

3. A daily record of his general condition as follows (Lawther, 1958): (*a*) condition better than usual, (*b*) condition the same as usual, (*c*) condition worse than usual, and (*d*) condition much worse than usual.

Arrangements were also made for health visitors to make two visits per month to each patient to inspect sputum and report progress. Finally, at the same pre-trial interview, the almoner calculated average daily earnings based on the number of working days per week; nasal swabs were taken and patients were given one month's supply of capsules with written instructions. Further supplies were issued each month.

At the end of each month of the trial progress was assessed by the chest physician, who recorded the number of attacks, their duration, and the working days lost in consequence. His assessments were made on the basis of patients' personal histories, their diaries, and the health visitors' fortnightly reports. The almoner recorded money-equivalents of working days lost and sums received from National Insurance, National Assistance, and other sources. At the end of the trial period, weekly tobacco consumption was recorded and further nasal swabs were taken. All diaries, chest physicians', health visitors', and almoners' reports were then forwarded for analysis.

Statistical Methods

The randomization of treatments was carried out regardless of the clinic to which the patient belonged, and no attempt was made to equalize the proportions in the treatment groups for each clinic. This step was taken deliberately, as it was felt that the clinical assessment of the patient's condition was highly subjective and that the chance of a clinician or health visitor guessing the treatment should be made as small as possible. For this reason also the capsules issued were not divided up into three distinct groups but allotted code numbers, which differed for every bottle of capsules. Randomization was carried out centrally and a supply of bottles sent out monthly to the clinics, each bottle being already labelled with the patient's name.

The lack of balance among the treatments which resulted from the randomization procedure was aggravated in some clinics by the withdrawal of some patients from the trial (see below). A detailed comparison of various characteristics of the patients, such as age, average earnings, whether indoor or outdoor workers, smoking habits, and previous claims for

TABLE I.—*Comparison of Various Characteristics of Control and Treatment Groups. There are No Statistically Significant Differences Between the Three Groups in Any of These Characters*

	Penicillin	Tetracycline	Control
Average age (years) ..	53	51	54
indoor employment ..	62	62	52
Average days lost in previous years	85	89	76
Averages wages per day ..	38/-	38/-	41/-
Cigarettes per week ..	54·1	54·7	55·3

sickness benefit, is summarized in Table I. There are no significant differences in any of these between the three groups. The excess of outdoor workers among the controls, and their smaller previous loss of time from bronchitis, are in any case such as to lessen any apparent benefit derived from treatment.

It is felt that systematic bias in favour of one or other type of treatment has been effectively removed, and that any errors of assessment and execution probably affected each group equally.

The technical details of the statistical analysis are given in Appendix I, as they are only of specialist interest.

Four measures of the effect of treatment were examined: these were (*a*) number of attacks, (*b*) duration of attacks, (*c*) days off work, and (*d*) money lost while off sick.

The number of attacks was found to be unaffected by the treatments, and the measure finally chosen for expressing the results was the total days off work due to attacks conforming to the definition during the period of the trial. Though closely correlated with the total duration of attacks, this is the more objective measure and showed less variation from clinic to clinic. Moreover it was checked later against Ministry of National Insurance records. It has also a direct meaning in economic and personal terms, but a possible disadvantage is that it is a rather stringent criterion of incapacity, and a proportion of the patients who in fact benefited from the treatment may have recorded no days off work.

It would have been possible to use the money lost through sickness as a measure of effect, but this, though related to days off work, is affected by the differences in average earnings among the patients, which are irrelevant to the main study.

Results

Of the 252 patients enrolled in the trial, 26 were excluded from statistical analysis, 14 because they were unemployed throughout and could provide no information on days lost from work, and 12 because no adequate records were available on their progress. Most of the latter were classified by their clinicians as uncooperative and they withdrew at an early stage. The 226 cases remaining fell into two categories: 185 were continuously under observation and at risk during the trial, and 41 were only intermittently at risk because they entered the trial late owing to previous illness or were admitted to hospital from various causes, or had spells of unemployment. The method used to include the experience of these 41 cases was to express the results in terms of man days off work per man days at risk.

Days Off Work

Analysis of the 226 cases in employment showed that both penicillin and tetracycline are beneficial in reducing the days off work due to bronchitic exacerbations or pneumonic episodes (Table II). The average days off work per man-day under observation in the three treatment groups were: 0.066 ± 0.014, penicillin; 0.084 ±0.019, tetracycline; 0.171 ± 0.025, control. It appears, therefore, that both the antibiotics approximately halved the time off work, but did not differ significantly from each other.

Serious respiratory infection occurred in six of the cases included in this analysis, leading to admission to hospital, death, or subsequent failure to continue in the trial. In the analysis these cases were counted as exposed for the whole period over which their history was known and the days off work related to this period. Two of them were on tetracycline and the remaining four were controls. The two on tetracycline both became very ill within a few days of entering the trial and can hardly be considered to have had effective prophylactic treatment at all. Of the four controls one died and the others were rather severe cases, and, taken as a whole, the inclusion of this group probably exaggerated the effects of antibiotic treatment.

TABLE II.—*Average Days Lost From Work Per Day Under Observation in the Three Treatment Groups for Each Clinic Taking Part in the Trial. Figures in Brackets are Numbers of Patients in Each Group*

	Penicillin	Tetracycline	Control
Cambridge	0·0681 (6)	0·1627 (6)	0·1543 (4)
Chertsey	0 (1)	0 (0)	0·0638 (3)
Croydon	0·0626 (5)	0·1680 (6)	0·2615 (6)
Dudley	0·0188 (6)	0·0907 (7)	0·0783 (7)
Dundee	0·0109 (4)	0·0203 (3)	0·0122 (5)
Edmonton	0 (1)	0·1203 (12)	0·0770 (6)
Finchley	0·0435 (4)	0·0058 (3)	0·8889 (1)
Ipswich	0·0017 (5)	0·1174 (4)	0·1725 (10)
Islington	0·1648 (2)	0 (5)	0·0087 (5)
Mansfield	0·1868 (5)	0·0029 (3)	0·5553 (7)
Preston	0·1551 (6)	0·0725 (3)	0·0250 (4)
Reading	0·0490 (11)	0·0671 (7)	0 (1)
St. Albans	0·0435 (2)	0·1101 (6)	0·1261 (2)
Tunbridge Wells ..	0·0435 (7)	0·0435 (4)	0·8348 (1)
Walthamstow	0·0580 (6)	0·0739 (4)	0·0609 (7)
Willesden	0 (2)	0·0304 (6)	0·2135 (5)
	0·0657 (73)	0·0838 (79)	0·1713 (74)

Penicillin, 0·0657 ± 0·0140. Tetracycline, 0·0838 ± 0·0187. Control, 0·1713 ± 0·0246. Differences (control − penicillin) = 0·1056 ± 0·0282. Differences (control − tetracycline) = 0·0875 ± 0·0309.

A separate analysis was also made of the 185 cases under observation continuously throughout the trial. Though this group may not be fully representative of the patients as a whole, it was felt that the analysis of the whole series might have given undue weight to the experience of those with very short exposures, and a more thorough statistical treatment is possible of the records concerning patients exposed throughout the trial. The benefits of antibiotic treatment are equally evident in this group, but the apparent superiority of penicillin over tetracycline disappears, being mainly due to the inclusion of one or two particularly unfavourable cases. The mean days lost per days at risk are as follows: penicillin, 0.06; tetracycline, 0.06; control, 0.12. The average days off and the average duration of attack per patient were:

Regimen	Days Off Work	Duration of Attack in Days
Penicillin	6·8	9·0
Tetracycline ..	7·5	11·5
Control	14·2	21·3

As in the main analysis, both antibiotic treatments led to halving of time off work compared with the control group.

Though the general benefit of treatment has been established its numerical value is not very accurately estimated. The variability of the days lost from work by patients in the same clinic and on the same treatment is very large; this is an important feature of the results, since it implies that they are only applicable on the average for large numbers of patients.

The approximate equal efficacy of penicillin and tetracycline is an unexpected finding, since the former is considered to have little effect on organisms of the *Haemophilus* group. From a statistical point of view the variability in response is so high that the true value of the difference between the two antibiotics is very inaccurately estimated, the errors of estimation being such that the observed difference is compatible with either drug having a saving of some four working days over the other.

Number of Attacks

The second interesting feature of the trial is that the treatments appear to have no effect in reducing the number of attacks per patient. For those patients who were under observation through the whole period of the trial the average numbers of attacks were as follows: penicillin, 0.92; tetracycline, 1.07; control, 1.04. The small differences are quite insignificant statistically.

Loss of Money

The loss of money due to the disease is of course highly correlated with the time off work and is made up of wages not earned, national assistance, and insurance payments from the State or private clubs and societies, the latter being a comparatively minor source in the present study. The average monetary losses per patient in the three groups were: penicillin, £14; tetracycline, £18; control, £40; and, as with the time off work, the effect of treatment was to halve the losses, penicillin and tetracycline being approximately equivalent.

The two drugs differ considerably in price, and the costs of treatment (calculated from retail prices in the *Prescribers' List of Proprietary Medical Products*, 1959) for the four-months period were about £32 for tetracycline and £16 for penicillin. The net costs for the three groups of patients during the four months of the trial were therefore as follows:

	Penicillin	Tetracycline	Control
Average money losses	£14	£18	£40
Cost of drugs	£16	£32	—
Net costs	£30	£50	£40

Compared with the control group there was an average net gain per patient of £10 (£40 down to £30) in the penicillin group; whereas in the case of the tetracycline-treated group there was a net less of £10. These considerations are apart from any question of the benefit of treatment to the patients.

Treatment by General Practitioners

Practitioners were asked to inform chest physicians whenever they prescribed chemotherapy, and the latter were asked to report such treatment each month. The numbers of treatments in 185 patients exposed to risk for the whole period were as follows:

	Treatments by General Practitioners		
	Total	<1 Week	>1 Week
Penicillin group	7	5	2
Tetracycline ,,	13	10	3
Control ,,	9	8	1

Side-effects of Treatment.—During the trial all patients were repeatedly asked by health visitors and chest physicians if they thought the treatments were causing side-effects. Thirty-five positive answers were received, the symptoms being mostly mild and transitory and occurring nearly always very early in the trial. Only six patients withdrew from the trial on this account, four of these being "control" cases. In none of the men taking antibiotics were side-effects of a serious nature. Gastro-intestinal symptoms consisted in the main of loose motions for a few days; other symptoms were mainly transient rashes and headaches. The information on side-effects is summarized in Table III.

TABLE III.—*Numbers of Patients Complaining of Toxic Symptoms in the Three Treatment Groups*

	Penicillin		Tetracycline		Control	
	W	NW	W	NW	W	NW
Gastro-intestinal	0	5	0	8	2	7
Other	2	4	0	5	2	0
Total	11		13		11	

W = Withdrawn from trial. NW = Not withdrawn from trial.

Deaths: Three deaths occurred among the 252 patients. Two were in the tetracycline group, both being due to pneumonia and cardiac failure. One patient in the control group died of acute-on-chronic bronchitis with emphysema and hypertensive heart disease. A further patient who started treatment with tetracycline died of carcinoma of the lung. The first three deaths occurred within two weeks of the start of the trial and the death from carcinoma took place on February 6, 1959.

Discussion

The benefits of the treatment given are largely confirmatory of previous work. Two findings are unexpected: first, that the improvement was in the duration rather than the number of exacerbations, and, secondly, the apparently equal efficacy of penicillin and tetracycline in the doses used.

The first of these could have arisen because the antibiotics acted as therapeutic rather than prophylactic agents, ensuring prompt treatment of the attacks without preventing them. It is also possible that their effect was to control secondary infection, the attacks themselves being precipitated by some other cause, such as a virus infection or some meteorological factor.

The main factors taken into account in choosing the doses of the antibiotics used in this trial were the nature of the pathogenic organisms likely to be important and the cost of the drugs. The most important pathogenic bacteria in chronic bronchitis are known to be *Haemophilus influenzae* and the pneumococcus. Pneumococci are always highly

sensitive to penicillin, but *H. influenzae* is seldom inhibited *in vitro* by concentrations lower than 1.25 u./ml., and bronchial infections caused by it respond to intramuscular penicillin G only in doses of 8 mega-units or more per day (Goslings and Hers, 1953) or to "estopen" in doses of 2 mega-units a day (May, 1955). Oral penicillin V, therefore, at a dosage level equivalent to 1 mega-unit daily, as prescribed in the trial, could only be expected to combat infections caused by pneumococci. As regards tetracycline sensitivity, the disparity between the two organisms is not so great, though the pneumococcus is still the more sensitive. The dose usually required to suppress *H. influenzae* in patients with bronchitis is 0.5 g. b.d. or higher (Helm *et al.*, 1954; May and Oswald, 1956), but, owing to the high cost of this drug, and to reports of encouraging results with chlortetracycline using a dose of 0.25 g. b.d. (McVay and Sprunt, 1953), the lower dose was chosen. It was hoped that both drugs would, in the doses used, suppress pneumococci, and that tetracycline might in addition suppress a reasonable proportion of *H. influenzae* strains.

Bacteriological examination of the sputum of patients in this trial was considered impracticable and was not carried out; interpretation of the results, therefore, can only be speculative. The most probable explanation, however, of the apparently equal efficacy of penicillin and tetracycline in shortening exacerbations is that only pneumococci were suppressed, the dose of tetracycline being inadequate to inhibit more than an occasional strain of *H. influenzae*. If this were so, exacerbations caused by the latter organism would remain uncontrolled in all treatment groups. Another possible explanation is that exacerbations caused by pneumococci were exceptionally prevalent during the months of the trial, but no reports to this effect have been received. In any case, even if this were so, tetracycline would still be expected to be the more effective drug if the dose were sufficient to suppress *H. influenzae* as well.

It seems probable, therefore, that this trial has in fact measured the value, both clinical and financial, of prophylaxis with particular doses of penicillin or tetracycline against pneumococcal exacerbations of bronchitis, and clearly, if this is the correct bacteriological interpretation of the results, the high cost of tetracycline makes its routine use *in the manner and dosage used in this trial* unjustifiable; but it cannot be assumed that the use of tetracycline in higher doses would not produce a better result than penicillin. Attempts are being made, in a second trial of prophylactic chemotherapy in chronic bronchitis, to carry out a bacteriological survey in order to facilitate interpretation of clinical results.

A comparison of the Ministry of Pensions and National Insurance records of the patients during and before the trial period shows that the period under review was not exceptional, and as the trial was carried out in a variety of places all over the country in both rural and industrial areas, it seems fair to conclude that the results are likely to have general application.

The conclusions arrived at on the financial aspects of treatment depend to some extent on how far the patients in the trial are a representative sample of all bronchitics. The patients were selected according to certain criteria in the first place, and there was further elimination of patients unemployed during the course of the trial. Similar savings can be expected only in similarly chosen patients, and the financial benefit of treatment might be greatly reduced by the inclusion of patients whose condition was not in fact improved by antibiotics.

It should be emphasized that the results can only be expected to apply on the average to a similar group of patients. In any individual case or small group of patients the effect of treatment may be disappointing. It has not been possible to single out any particularly suitable type of patient; two important objects of future study would be to define more closely the type of patient to whom these conclusions apply and to investigate the effects of other techniques of administering antibiotics.

It might also be objected that treatment affects only exacerbations of bronchitis, as defined here, and pneumonic episodes, and that alleviation of these may be compensated by a corresponding increase of other respiratory disability. In fact, time lost from work due to respiratory illness as a whole, recorded by the Ministry of Pensions during the period of the trial, was very close to the losses as recorded by the chest physicians:

	Average Loss per Patient in Days		
	Penicillin	Tetracycline	Control
All respiratory causes ..	7·8	8·4	14·9
Causes as defined in trial	6·8	7·5	14·2

Clearly, in this type of patient the greater part of respiratory disability is accounted for by exacerbations as defined in this trial.

Summary

A controlled trial has been carried out to estimate the usefulness of penicillin and tetracycline as long-term prophylactics in chronic bronchitis.

Information was specially collected to determine the monetary losses from the disease in relation to the cost of treatment.

It was found that 312 mg. of penicillin V twice daily or 250 mg. of tetracycline twice daily approximately halved the days lost from work as compared with a control group receiving an inert treatment. Tetracycline did not differ significantly in its effect from penicillin, but the cost of treatment was much greater.

Neither drug significantly reduced the number of attacks of bronchitis. The validity of the results is discussed, and it is concluded that the method of study used was reliable.

The committee wishes to acknowledge with thanks the co-operation and help of: Mr. E. A. G. Cook, of Eli Lilly & Co., Ltd., who supplied the penicillin V and encapsulated and bottled all the materials used in the trial; Mr. J. R. Wilson, F.R.C.S., of Lederle Laboratories, who supplied the tetracycline; the Ministry of Pensions and National Insurance for their co-operation in supplying information relevant to the patients participating in the trial; the chest-clinic physicians, their medical staff, health visitors, and almoners; the numerous general practitioners who co-operated in the trial; the bacteriologists who cultured nasal swabs; Doreen Harmsworth for technical

assistance in carrying out sensitivity tests; and finally, to Jean Goodchild and Jean Corton for secretarial assistance.

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APPENDIX I (Statistical)

A preliminary study of the results showed at once that there was little difference between the groups in the numbers of attacks per patient. There were considerable differences between the treated and controls in duration of attack, days off work, and money lost. However, an analysis of the former on the lines indicated below showed a considerable variation between clinics in the assessment of duration, and the days off work were finally chosen as the best index of treatment.

The distribution of days off work per patient is J-shaped with a maximum at 0 and a long tail extending up to 100. In addition there was a correlation between variance and mean, the untreated with a larger mean being much more variable. A plot of the probits of the cumulative frequencies against log time, however, was approximately linear, the two treated groups having probit lines parallel to the untreated but with smaller means. It seems from this that the treatment affects the whole population and not just a group of particularly sick patients.

The presentation of the results in the main text ignores the differences between clinics and simply gives the mean days off work per days of exposure and their standard errors, from which the significance of the differences between means can be assessed. This is justifiable since it is shown below, in an analysis of the patients oberved throughout, that the differences between clinics were negligible.

The analysis of the results for those at risk all through the trial presents itself most naturally as an analysis of variance with unequal numbers in each subclass. This is appreciably more laborious to carry out than in the ordinary case when the numbers are equal, but presents no difficulties of principle or calculation. The methods used are well described by Snedecor (1946, Chapter 11).

The analysis was carried out after transforming the days off (x) to a variable y such that $y=\log_{10}(1+x)$. This considerably reduced the correlation between variance and mean but could not affect the essential skewness of the distribution.

The analysis of the transformed variates was done in two parts: first, constants were fitted for clinics and treatments and an estimate was made of the interaction term. This was found to be quite insignificant compared with the variance of patients on the same treatment at the same clinic, the analysis of variance table being as follows:

	S.S.	D.F.	M.S.
Constants (clinics + treatments)	10·5378	16	0·659
Interaction	11·4800	28	0·410
Within subclasses	51·161	140	0·365

The effect of fitting constants is significant at the 5% level and the interaction is not. The separate effects of treatments and clinics were tested by a weighted analysis of variance summarized in the following table:

	S.S.	D.F.	M.S.
Clinics	5·1723	14	0·369
Treatments	2·3850	2	1·193
Within subclasses	51·161	140	0·365

The mean square for clinics is almost exactly the same as the error term and not statistically significant, but the effect of treatment is significant at the 5% point.

APPENDIX II

THE INFLUENCE OF CONTINUOUS CHEMOTHERAPY ON THE CARRIAGE OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI IN THE ANTERIOR NARES

Though coagulase-positive staphylococci play only a very minor part in chronic bronchial infections, an increase in the nasal carrier rate of antibiotic-resistant strains in bronchitics receiving continuous chemotherapy would be important inasmuch as it would add to the general reservoir of resistant staphylococci in the population as a whole.

Collection of Specimens

The anterior nares of each patient were swabbed by chest physicians at the beginning and end of the trial. Swabs were soaked in nutrient broth before use and forwarded as soon as possible to the local bacteriologist for culture. Any coagulase-positive staphylococci isolated were sent to the Bacteriology Department, Institute of Diseases of the Chest, for sensitivity testing.

Sensitivity Testing

Sensitivity to penicillin and tetracycline was estimated by titration in nutrient broth. In order to minimize experimental error the following precautions were taken: (*a*) All tests were performed by one person. (*b*) The staphylococci were tested in batches, dilutions of the antibiotics being prepared in bulk and then distributed into the appropriate number of sets of test-tubes for the individual organisms. (*c*) A control titration using a standard organism (the Oxford staphylococcus) was performed with each batch of tests. (*d*) All staphylococci isolated at the beginning of the trial were preserved on agar slopes, and those derived from patients from whom staphylococci were subsequently isolated at the end of the trial were retested in parallel with the latter.

Sensitivity to tetracycline was tested over the range 10 to 0.3 μg./ml. in doubling dilutions. That to penicillin was tested initially from 0.5 to 0.01 u./ml., and any organism resistant to this range was retested over the range 10 to 0.3 u./ml.

Definition of "Sensitive" and "Resistant."—The selection of a sensitivity level above or below which a given organism might be classed as "sensitive" or "resistant" must necessarily be somewhat arbitrary. In fact, however, the sensitivities fell very clearly into two groups for each antibiotic: (*a*) Penicillin, resistant to 10 u./ml. or sensitive to 0.5 u./ml. or less; (*b*) tetracycline, resistant to 10 μg./ml. or sensitive to 1.25 μg./ml. or less. These concentrations were accordingly selected to distinguish between "sensitive" and "resistant" strains for the purposes of the present report.

Results.—Results have been compiled only in relation to those patients who completed the trial (see main report). Further, some clinics failed to take nasal swabs both at the beginning and at the end of the trial, and the patients attending these clinics have therefore had to be excluded from parts of the analysis.

The basic results obtained at the beginning of the trial are shown in Table A. They represent the current situation as regards nasal carriage of staphylococci in chronic bronchitics in the country as a whole and are in no way remarkable. The results obtained at the end of the trial (10 clinics only) are shown for comparison. They reveal little change in the carrier rate, but there is a slight relative increase in the rates of antibiotic-resistant organisms,

TABLE A.—*Nasal Staphylococcal Carrier Rates at the Beginning and End of the Trial*

	No. of Clinics	No. of Patients	Coagulase-positive Staphylococci		
			No. Isolated	No. Resistant to:	
				Penicillin	Tetracycline
Before trial	15	180	38 (21%)	4 (2%)	3 (2%)
After ,,	10	134	25 (19%)	6 (5%)	10 (8%)

especially those resistant to tetracycline. Little significance can be attached to these results, however, since they take no account of the treatment to which each patient had been exposed.

Results in Different Treatment Groups

More detailed analysis of the results in relation to treatment groups is given in Table B. It is unfortunate that the distribution of staphylococcal carriers at the beginning of the trial was not uniform between the three treatment groups, but the trends within the groups are clear. While the control group showed a slight rise in the carrier rate, there was a corresponding fall in each of the treatment groups. In both the latter, however, the *relative* number of staphylococci resistant to the particular antibiotic rose. This rise was significant in the case of tetracycline, but not significant in the penicillin group.

TABLE B.—*Results in Different Treatment Groups*

Treatment	No. of Patients	Beginning of Trial			End of Trial		
		No. of Staphs.	R. to P.	R. to T.	No. of Staphs.	R. to P.	R. to T.
Penicillin	42	13 (31%)	2 (5%)	1 (2%)	9 (21%)	3 (7%)	1 (2%)
Tetracycline	49	12 (24%)	1 (2%)	0 (0%)	8 (16%)	2 (4%)	8 (16%)
Control	43	4 (9%)	0 (0%)	0 (0%)	8 (19%)	1 (2%)	1 (2%)
Total ..	134	29 (22%)	3 (2%)	1 (1%)	25 (19%)	6 (4%)	10 (7%)

All percentages referable to number of patients in relevant treatment group. R. to P. = Resistant to penicillin. R. to T. = Resistant to tetracycline.

Changes in the Carrier State of Individual Patients

Coagulase-positive staphylococci were isolated from the anterior nares, both at the beginning and at the end of the trial, of 14 patients. Of these, nine were treated with penicillin, four with tetracycline, and one was a control. The sensitivity patterns remained unchanged after the trial in the single control patient and in eight out of the nine penicillin-treated patients. The staphylococcus isolated after the trial from the remaining penicillin-treated patient was resistant to penicillin and sensitive to tetracycline, whereas that found before the trial had been sensitive to both antibiotics. In contrast, each of the four staphylococci isolated from the tetracycline-treated patients after the trial was resistant to tetracycline (but sensitive to penicillin), whereas before the trial fully sensitive strains had been isolated in each case.

Though these figures are small there was clearly a greater tendency for sensitive strains to be replaced by resistant ones in the tetracycline-treated group than in the group receiving penicillin.

In a further 11 patients staphylococci were found after the trial but not before it. Four of these patients were treated with tetracycline, and each corresponding staphylococcus was resistant to this antibiotic; two were also resistant to penicillin. No patients receiving penicillin fell into this group, but of the seven staphylococci isolated from controls five were sensitive to both antibiotics, one was resistant to tetracycline and sensitive to penicillin, and one was resistant to penicillin and sensitive to tetracycline.

Conclusions

The development of antibiotic-resistant staphylococci in the anterior nares was not a serious problem in this trial, but when it did occur it was almost exclusively in response to tetracycline. Sixteen per cent. of the patients treated with tetracycline were nasal carriers at the end of the trial and in each case the staphylococcus was resistant to this antibiotic. At the beginning of the trial there were no carriers of tetracycline-resistant staphylococci in this group.

In contrast, the penicillin-treated group showed an increase of from 5% to 7% in the carrier rate of penicillin-resistant staphylococci—an increase similar to that in the controls.

Development of tetracycline-resistance in patients treated with penicillin was never observed. But in two patients treated with tetracycline staphylococci resistant to both drugs were found at the end of the trial.

COLD INJURY IN THE NEWBORN

A STUDY OF 70 CASES

BY

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Though the clinical picture of cold injury in the newborn had been described as early as 1889 by Henoch, and has been recognized by individual paediatricians in this country for some years (Braithwaite, 1955; Smallpeice, 1955; Everley Jones, 1955; Williamson, 1955), it was Mann who first gave a full description of the syndrome and made recommendations for its prevention (Mann, 1955; Mann and Elliott, 1957).

The condition is still not as widely recognized as it should be and it is not described in current paediatric textbooks. Though preventable, it still occurs and is often undiagnosed; this survey of all newborn babies with cold injury admitted to the Children's Hospital, Birmingham, in the years 1946–56 has therefore been made. We describe the clinical features, the aetiological factors, and the results of a follow-up investigation of those who survived.

Material

Though the diagnosis of chilling as the cause of illness in newborn babies was not often made in this hospital before 1951, we included in our initial survey all babies admitted during the years 1946–56 whose rectal temperatures were less than 96° F. (35.6° C.) at some time during the first 24 hours after admission. In this way we hoped to discover not only the incidence of hypothermia due to chilling but also the frequency of hypothermia in other diseases of the newborn. Thermometers registering temperatures below 95° F. (35° C.) were not in use before 1951, so that in the early years even the temperatures of severely chilled babies were recorded as "95" or "below 95."

The total number of such patients was 183. The diagnoses are shown in Table I; in nearly all cases they were unequivocal and in only seven did we feel sufficient doubt about the diagnosis to regard the case as unclassifiable. When hypothermia is not primarily due to external chilling or to prematurity the illness is severe and diagnosis of the primary disease is not difficult. Moreover, post-mortem confirmation of the

TABLE I.—*Diagnoses of All Neonates With a Temperature Reading Below 96° F. (35.6° C.) in the First 24 Hours After Admission* (1946–56). (183 *Patients*)

Primary cold injury	70
Prematurity	48
Cerebral birth injury	23
Severe infection	15
Congenital heart disease	6
Perinatal asphyxia	9
Severe malnutrition	3
Paroxysmal tachycardia	1
Infection and cerebral birth injury	1
Unclassifiable	7

diagnosis was obtained in 33 of the 54 cases classified as cerebral birth injury, infection, congenital heart disease, or perinatal asphyxia. (Those premature babies with additional disorders such as cerebral birth injury and asphyxia are included in the prematurity group.) The cases classified as "primary cold injury" were not, however, given this label merely because of the absence of other diagnosable disease. Even in the earlier years, when we did not personally see the patients and low-reading thermometers were not in use, the hospital case-notes contain enough of the characteristic clinical features to make the diagnosis reasonably certain. Not all these babies were free from infection, but the infection, when present, was minor, and any case in which it was thought that the infection was more serious and played a substantial part in causing hypothermia was placed in the "severe infection" group. In such cases the characteristic features of "primary cold injury"—for example, facial redness—were not found.

Only three premature babies have been included in the "primary cold" group. Small premature babies are relatively thermolabile, and a moderate hypothermia does not necessarily represent a pathological state as it does in the mature infant. A temperature of 91–96° F. (32.8–35.6° C.) may be as satisfactory for the small premature baby as one of 96–98° F. (35.6–36.7° C.), and the diagnosis of "cold injury" must be applied with caution to premature babies. In the early years of this review period it was the practice to admit premature babies to this hospital solely on account of prematurity, and many of these babies were in reasonably good condition on admission and remained so. The three premature babies who have been included in the category of "primary cold injury" were over 5 lb. (2,270 g.) at birth and were severely chilled. Environmental factors seemed to be responsible for their hypothermia.

The relatively high incidence of hypothermia due to cerebral birth injury is perhaps not surprising. The thermoregulatory centres are liable to be affected under these circumstances, particularly when the injury is severe. Of these 23 patients, 18 (78%) died, and in the 15 on whom necropsy was performed intracranial haemorrhage was found. The high fatality rate suggests that hypothermia is a grave sign in cerebral birth injury.

Hypothermia in congenital heart disease is also of grave significance. All six babies in this group died. Necropsy showed a severe form of heart disease in all, and, though external chilling may have been a contributory factor, it is reasonable to assume that the cardiac lesion itself was mainly responsible for death. One infant, in whom no cardiac lesion was suspected and who was classified under "primary cold injury," was found to have a septal defect at a follow-up examination. His case is discussed later. It seems unlikely that his cardiac lesion played any part in the occurrence of hypothermia.

Primary Cold Injury (70 cases)

The clinical features of this condition are well illustrated by the following two cases.

Case 1

Derek was born at full term on January 31 at home. The delivery was normal, and his birth weight was 7 lb. (3,175 g.). His condition after birth was good; he cried immediately. He was bathed and put into a cot with several blankets and a hot-water bottle. The cot was kept near the coal fire, which was burning day and night. On the day of his birth snow had fallen, and the maximum air temperature was 21° F. (−6.1° C.), the minimum 17° F. (−8.3° C.).

The midwife noticed that he was cold in the first 12 hours. After the first day he would not suck and he became more lethargic until he was admitted to hospital at the age of 3 days. His rectal temperature was 85° F. (29.4° C.). His body had a mortuary coldness. He lay quietly, and his face looked healthy because the complexion was florid. The hands and feet were pink and oedematous, and the cheeks and buttocks were hard with sclerema. There were no signs of infection.

Progress and Treatment.—He was nursed, normally clothed, in a Sorrento cot in a cubicle kept at 65–70° F. (18.3–21.1° C.). He was fed by a gastric tube with 5% dextrose. He slowly became more active and his temperature rose over the next three days. He passed no urine for the first 24 hours and his blood urea then was 135 mg./100 ml. Sclerema persisted for five days and oedema for a further six. The blood urea was normal before discharge. When examined at the age of 15 months he was physically and mentally normal.

Case 2

Andrew was born at full term on January 18 at home. His birth weight was 8 lb. (3,630 g.). The delivery was easy and he cried immediately. There was some delay in attending to him because of the midwife's concern with the mother, who had a post-partum haemorrhage. He was bathed, clothed, and put in a cot with several blankets and hot-water bottles. Outside there was snow on the ground and the maximum air temperature in the first day of life was 33° F. (0.6° C.), the minimum 27° F. (−2.8° C.). The cot was kept at the foot of the bed between the window and the fire, which was allowed to die at midnight and was rekindled at 7 o'clock each morning.

He was slightly cyanosed on the first day and the cyanosis increased over the next three days. His feet and ankles were swollen on the day before admission. The rectal temperature on admission was 86° F. (30° C.). His skin was deathly cold. He was inactive. The face was ruddy and looked healthy. The feet and hands were oedematous and slightly cyanosed. The buttocks were hard with sclerema. There was no evidence of infection. With the same treatment as the first patient received, the sclerema disappeared within two days and the oedema after a week. He suffered no ill effects and was physically and mentally normal when examined at the age of 2 years 3 months.

Aetiology

A low environmental temperature has been emphasized by previous authors as the most important aetiological factor, and our inquiries fully confirm this.

External Temperature

Fig. 1 shows the minimum air temperature recorded at Edgbaston Observatory on the day before the onset of symptoms in each patient. All patients came either from Birmingham or from places within a 15-mile (24-km.) radius of the city, so that the figures are a good guide to external temperature at the time of the

occurrence of cold injury in each baby. It will be seen that the temperature in 53 instances out of 70 was below 35° F. (1.7° C.). Fig. 2 shows the number of patients whose symptoms started in each month of the year. Fifty-six occurred in the months of January, February, and March. Finally, inquiry from the mothers of the 31 survivors whom we were able to trace (it was not felt justifiable to question the parents of the babies who died) showed that in 17 cases there was snow and ice on the day of birth, and in a further six cases the weather was said to have been "bitterly cold."

The occasional occurrence of cold injury at relatively high air temperatures is of interest. There were seven examples where minimum air temperatures were 44° F. (6.7° C.) or over (one in March, one in April, one in May, one in June, one in September, and two in November). The symptoms and signs in these patients were characteristic, and in the one fatal case the necropsy findings were in keeping with the diagnosis. Three of these babies had long histories (two to three weeks). Chilling was apparently more gradual than usual, as one might expect with air temperatures which were not very low. Another baby had prolonged physiological jaundice, which may have interfered with internal thermoregulation. The remaining three patients were less than 5 days old, and no reason can be found for their hypothermia. Farquhar (1957) mentions similar cases.

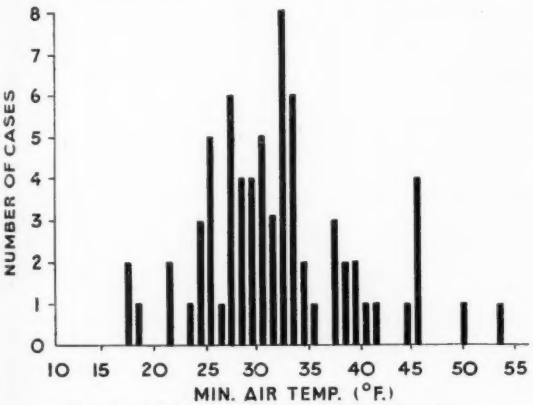

FIG. 1.—Minimum air temperatures (70 cases).

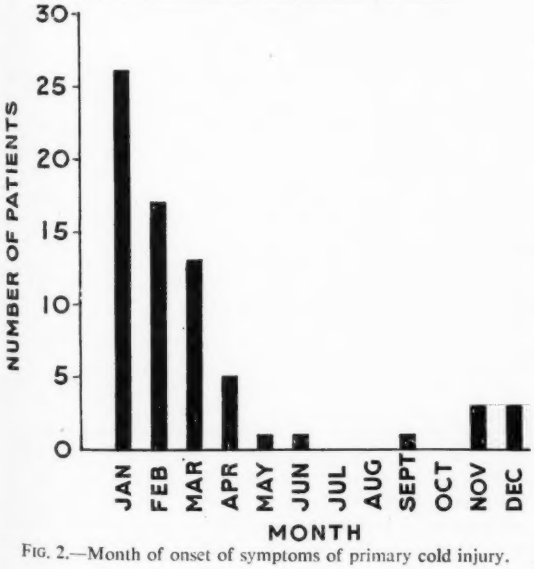

FIG. 2.—Month of onset of symptoms of primary cold injury.

Room Temperature

The average bedroom in this country is heated inadequately or not at all, so that its temperature to a large extent reflects the external temperature. A coal fire is usually allowed to die at night, or an electric fire is switched off when the family goes to bed. Though conditions may be modified for the new baby, it may not be realized that he is less able to withstand the low temperatures of the early morning than are older children and adults. Draughts from an ill-fitting closed window may also lower the bedroom temperature.

At the follow-up examination of 31 of the survivors we attempted to get some idea of the incidence of such factors by questioning the mother about environmental conditions in the affected infant's first few days of life. In spite of the lapse of time, many mothers answered readily, and we felt that the drama of the baby's illness had impressed these facts upon their minds and that their answers were fairly accurate. Of the 25 born at home, in 11 cases the mothers remembered either that the coal fire had been allowed to die at night or that the electric fire was switched off. (One of the two babies born in a hospital had been put into a newly opened ward with no heating; four had been born in nursing-homes; the heating arrangements in these institutions are unknown to us.) We were unable to obtain accurate information about the position of the cot in relation to open windows or other sources of draughts, but it was often next to the mother's bed, away from the fire. All babies were nursed in cots. It has been pointed out (Smallpeice, 1955) that the general fear of overlaying does not allow the baby to be nursed in the mother's bed, though this traditional practice might prevent neonatal chilling.

Other External Factors

Though it appeared that the babies were adequately clothed, it is not perhaps realized that clothing and blankets may be insufficient to protect a baby from the effects of a cold room. They may in fact accentuate chilling. Tight wrapping ("cocooning") may restrict muscular movement and peripheral circulation; and the wrappings may act as efficient insulators and keep the baby cold when the room temperature rises after the fire is relit in the morning.

Cold injury may be initiated within the immediate post-partum period if chilling is allowed to occur then. If the midwife is busily attending to the mother, or the baby is born before the midwife's arrival, he may be exposed to a low room-temperature for several minutes, and it is not difficult to imagine the severe effect of this sudden chilling on a body not conditioned to it. In only four of our cases was there a history of immediate exposure, but in 22 (31%) the baby was said to have been unwell from birth (Table II). This surprisingly high figure suggests that chilling at birth is more important than is generally realized. The ritual bath may also be an additional factor of importance, but we have no data on this point.

TABLE II.—*Day of Life on Which First Symptom Was Noticed*

	1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	–2 Wks	–3 Wks	–4 Wks	Indefinite
No. of cases	22	7	12	6	2	2	6	6	3	1	3

Inherent Factors in the Neonate

Why should a full-term newborn baby be unable to withstand such chilling? Relative lack of movement, perhaps exaggerated by tight wrapping, and immaturity of shivering mechanisms will cause diminished heat production. Poorly developed vasomotor reflexes (Herlitz, 1943; Bower, 1954, 1956), relative deficiency of subcutaneous fat, and a high ratio of surface-area to body-mass will increase heat loss. Refusal to feed, the commonest symptom, will aggravate cooling by failing to supply material for the increased katabolism necessary to counteract loss of heat. Prematurity might be expected to be a common predisposing factor, for all these factors are exaggerated in this condition. The fact that serious chilling is not very common in small premature babies is probably because doctors and midwives are well aware of the necessity of keeping a premature baby warm, whereas the necessity of guarding against chilling of the full-term neonate in winter is not generally appreciated.

History

It is unusual for the correct diagnosis to be made before admission to hospital, and it is still all too common for several days to elapse before any of the attendants realize that the baby is ill. We believe there are two main reasons for this. Firstly, the ruddy complexion of the baby gives a false impression of health (this is discussed below), and, secondly, the onset is usually insidious and there is no dramatic event, such as a convulsion, to alert the parent, the midwife, or the doctor.

Table III shows the frequency of the symptoms in the histories given by the parent or midwife, who often brought the baby to hospital. Slowness or refusal of feeds was, as in Mann's experience, the commonest symptom (73%). It is a common feature of all neonatal illness, and it is therefore unhelpful in leading the attendants to make a correct diagnosis. Nevertheless, if anorexia persists, it should lead to a search for more specific features. Lethargy and drowsiness (34%)

TABLE III.—*Primary Cold Injury—Frequency of Symptoms (70 Cases)*

Symptom	No.	Percentage
Slowness or refusal of feeds	51	73
Swelling (usually limbs)	37	53
Coldness to touch	25	36
Lethargy and drowsiness	24	34
Vomiting	12	17
Oliguria	9	13
Redness of skin	8	11
Jaundice	7	10
Haemorrhage	4	6
Hardening of tissues	4	6
Rigidity of limbs	2	3
Convulsion	1	1

have the same implication. The other two common symptoms, swelling (oedema), usually of the limbs (53%), and coldness to touch (36%), are more specific and, if present, should point to the diagnosis. Oedema was noticed by parent or midwife in as many as half the patients. Its usefulness as a pointer to the diagnosis should be emphasized, for other causes of oedema in full-term babies at this age, such as congenital heart disease and haemolytic disease, have their own recognizable features. Other characteristic signs, such as oliguria, skin reddening, and induration, were noticed less often, but when present they should suggest the diagnosis.

The ages at which the first symptom was noticed are shown in Table II. In the majority (81%) this was in the first week. Apart from the largest group, whose symptoms date from birth, the commonest age at onset was 3 days. This peak may, however, be misleading, since during the first two days a baby may be expected to be lethargic and unwilling to suck, and only at the end of that time may the parent or midwife suspect that he is unwell. Cold injury should be considered as a likely diagnosis in a baby, born at home in the first three months of the year, who in the first week of life refuses to feed. If this symptom occurs after the first week, other causes, such as infection or congenital heart disease, assume greater importance.

Clinical Picture

The important clinical features noted on admission are shown in Table IV. Their incidence in the total group is shown in the first column. In case the detection of these features had been more efficient in the last five years of the survey, when interest in the condition was greater, their incidence in the 35 patients

TABLE IV.—*Clinical Features Noted on Admission*

Clinical Feature	Total (1946–56) (70 Patients)		Recent Group (1952–6) (35 Patients)	
	No.	Percentage	No.	Percentage
Oedema	54	77	31	89
Immobility	41	59	21	60
Sclerema	27	39	14	40
Red face	31	44	16	46
Cyanotic face	11	16	7	20
Pale face	3	4	3	9

admitted in 1952–6 is given for comparison. It will be seen that there is little difference between their relative frequencies in the recent group and in the total group. The only noteworthy difference is in the frequency of oedema, which is greater in the recent group.

Oedema was the commonest sign, noted in 77% of the total group and 89% of the recent group. We have already emphasized its usefulness as a diagnostic feature when it occurs in a full-term neonate without signs pointing to other disorders. The term sclerema has caused much controversy. We have used it in Parrot's sense (quoted by Henoch, 1889): "An induration and rigidity which the skin of the infant offers to pressure . . . [the skin] loses its softness; and finally can no longer be raised from the subjacent parts, to which it appears firmly attached . . . [it] soon acquires the consistency of thick leather. All soft parts then appear as rigid as wood or stone; there is no pitting on pressure." It may be found on the cheeks, buttocks, or limbs, or it may be so widespread as to suggest a suit of armour. Respiration is very shallow and there may be real difficulty in passive movement of the limbs. Sclerema was noted in 39% of the total number, but its true incidence may have been higher.

Facial erythema, a striking feature, was commented upon in 44%, whereas cyanosis was mentioned in only 16%. These figures illustrate the frequency of a sign which is too apt to convey an impression of health to an unwary observer by comparison with cyanosis, a sign which in other states is more sinister. The erythema is presumably due to relative failure of dissociation of oxyhaemoglobin at low temperatures. The situation is analogous to that in pink disease, where the cold extremities are often pink rather than cyanotic.

Pallor was noted in only three cases, but we think it is commoner than this.

Once the body is palpated the coldness should be easily appreciated, and the combination of coldness and sclerema is in severe cases reminiscent of frozen meat. "There is an aura of coldness about the body," as Mann says, and the mother of a severely chilled baby told us that even the baby's breath was cold. Yet in the milder cases it is easy to miss the hypothermia, presumably because the medical attendant instinctively thinks of illness in terms of a raised temperature, and unless the possibility of this syndrome is borne in mind the coldness to touch may not be appreciated. It is still perhaps not fully realized that the standard clinical thermometer may also give a false impression, since a temperature below 95° F. (35° C.) will, of course, register as 95° or slightly higher, according to how

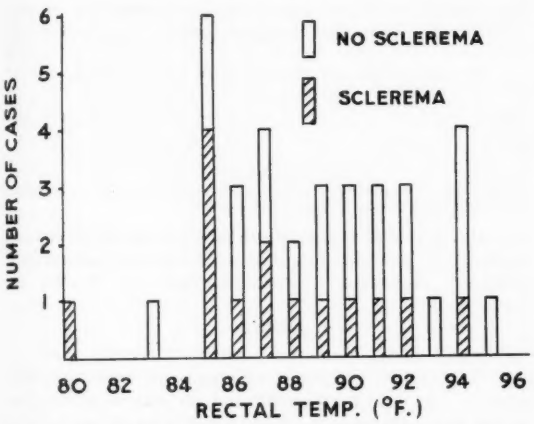

FIG. 3.—Admission temperatures and presence of sclerema (35 cases, 1952–6). White columns: No sclerema. Hatched columns: Sclerema.

vigorously the thermometer was shaken. In the early years of this survey many babies with typical clinical features were recorded as having admission temperatures of "95" or "below 95," and it was only when special low-reading thermometers were employed that the severity of the chilling was fully appreciated. The admission temperatures of babies admitted when low-reading thermometers were in use (1952–6) are shown in Fig. 3). The 35 whose temperatures were held to be true readings ranged from 80° to 95° F. (26.7 to 35° C.). The presence or absence of sclerema is shown in each case. We had hitherto considered it to be a sign of severe chilling, and were surprised to see that it was almost as common in those with relatively high temperatures as in those with low ones. Nor in our series could it be related to the length of history.

Immobility was commonly noted (59%). It is no doubt due partly to the general diminution of activity, but the splinting effect of large scleremato us areas must also be important. Some of these babies are literally "frozen stiff."

Oliguria is common in the first 24–48 hours after admission.

Sex Incidence.—There were 42 boys and 28 girls. This striking male preponderance was also found by Mann (1958) and Oppé and Simpson (1957), and is difficult to explain.

Investigations

In view of the parlous state of some of these babies, venepuncture and other disturbing procedures were usually avoided. However, blood was taken for chemical estimation in nine cases.

The only striking finding was an initial blood urea of 90 mg./100 ml. or above in the five babies whose initial temperature was below 89° F. (31.7° C.), while it was below 50 mg./100 ml. in three babies whose temperatures at admission were above 89° F. The remaining patient, whose admission temperature was not properly recorded, had widespread oedema and sclerema and was probably severely chilled; his urea was 134 mg./100 ml. Oliguria during the first few days was noted in five of the six severe cases but was not found in two of the three milder cases. High phosphorus and high potassium levels were found in two of the severely chilled patients. Two explanations of these findings are possible: that tissue breakdown was responsible, or that there was a gross diminution in glomerular filtration rate.

No other consistent biochemical abnormality was found, but the blood-sugar was not estimated. Mann and Elliott (1957) found severe hypoglycaemia in two out of six babies in whom the estimation was performed.

Treatment

There have been differences in the treatment of these infants over the years covered by this survey. It was soon discovered that rapid warming could lead to hyperthermia and convulsions, and vigorous warming was soon abandoned. The method employed over the last five years aims at raising body temperature gradually over several days. It is not unusual for this to take a week. The baby is admitted to a cubicle whose temperature range is 65–70° F. (18.3–21.1° C.), and is nursed fully clothed in a Sorrento cot. No extra clothing is used, except for a woollen bonnet. Hot-water bottles are kept in pockets on the sides and foot of the cot. Disturbance is kept to a minimum, in some cases even feeds being withheld for the first day. After this period tube feeding is used until one is sure that the baby is vigorous enough to take from a bottle.

We have been satisfied with slow warming in practice and have felt that its theoretical justification lay in the fact that by this method peripheral warming would not outdistance central warming. It has seemed to us undesirable that peripheral metabolism and oxygen need should be increased before the cardiorespiratory apparatus has been warmed sufficiently to cope with these demands. Even central warming (Polani, 1955; Farquhar, 1957) must be uneven in its effect, and we have favoured a method which will never cause steep temperature gradients between one part of the body and another.

Various antibiotics have been given routinely for prophylaxis and also because the clinical signs of infection may occasionally be absent and yet infection is revealed at necropsy. Additional oxygen has been administered only when cyanotic attacks occurred.

Additional glucose in gastric feeds (Mann and Elliott, 1957) has been given only occasionally, and from these few cases we cannot judge whether it is necessary.

It is not possible to compare the effect of various therapeutic measures in this retrospective survey, and

we cannot dogmatize on any of the above impressions. Even a prospective trial of slow warming against rapid warming would be difficult to carry out, in view of the difficulty of matching other factors such as length of exposure, type of exposure, initial temperature, severity of sclerema, etc. Nor would we feel it to be ethically justifiable.

Prognosis

Eighteen babies died, a mortality rate of 26%. On admission there seems to be no reliable indication of whether an individual baby is likely to survive. Though a very low initial temperature or the occurrence of sclerema is often followed by death, there are exceptions. Fig. 4 shows the initial temperatures of the

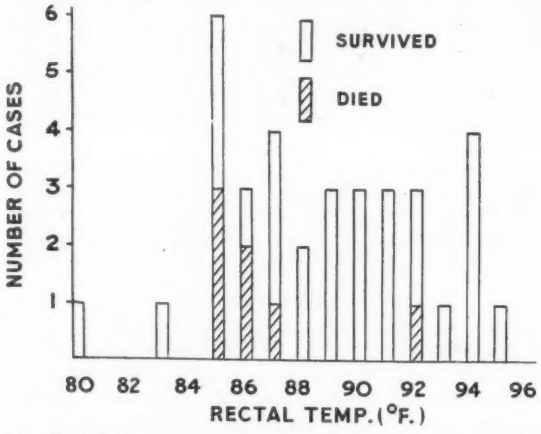

FIG. 4.—Admission temperatures and deaths (35 cases, 1952–6). White columns: Survived. Hatched columns: Died.

35 cases admitted in 1952–6, when low-reading thermometers were in use. Six of the seven deaths occurred in babies with temperatures below 88° F. (31.1° C.), yet the two babies with the lowest initial temperatures survived. Sclerema was found in five of the seven fatal cases, but nine babies with sclerema survived. Deaths were uniformly scattered over the years of the survey and could not be related to any particular change in treatment. There were seven deaths in boys (17%) and 11 in girls (39%).

Post-mortem examination was carried out in 15 of the 18 fatal cases. Macroscopic pulmonary haemorrhage was found in all, and in 11 it was the outstanding lesion. In the remaining four, infective lesions were also present; two had fibrino-purulent pleurisy and two had otitis media. One of the three in whom post-mortem examination was not performed had septic spots on the face for three days before death, and it is therefore possible that he had more serious infection elsewhere.

These findings are similar to those in the series of Mann and Elliott (1957), where five out of eight cases showed massive pulmonary haemorrhage, and infection was only an occasional finding.

Follow-up Survey

There is little information about the prognosis after survival of neonatal chilling. We therefore attempted to trace all survivors in the "primary cold injury" group, to examine them, and to interview their parents. We were able to do this in 31 cases. We obtained information about the subsequent history and the present mental and physical state by letter in three more cases where the child now lived at a distance. One other patient was examined for other reasons within a few months of discharge but could not be re-examined at the time of the survey. And one patient, having made a complete recovery, had died of leukaemia at the age of 2 years. Thus we had information about 36 of 52 survivors (69%), which we regard as reasonably satisfactory in this area, where there is always a considerable shifting population. A low-reading thermometer had been used in 23 of these 36; the admission temperatures of 13 were below 90° F. (32.2° C.), so that severe cases formed a significant proportion of the survivors. At the interview we inquired about general health, developmental milestones, comparison with other children in the family, and scholastic progress when the child was of school age. In addition we asked the specific questions about the circumstances of the child's birth which we discussed above. We carried out

TABLE V.—*Age at Follow-up Interview* (34 *Children*)

Age in Years	1–	1½–	2–	3–	4–	5–	6–	7–	8–	9–	10–	11–
Number ..	6	1*	4	4*	4	4	—	1	1	—	6*	3

* Postal information in 1 case.
In addition, one patient died aged 2 of leukaemia, and one was an ament with spastic quadriplegia when seen at 8 months.

a routine physical examination with special emphasis on neurological examination, and we measured heights and weights. The ages at the interview are shown in Table V.

Findings

Physical Development.—Twenty of the 25 children over 2 years of age were weighed and measured for height. The results were plotted on charts which use figures from the Oxford Child Health Survey and L.C.C. report of 1955 (Polani, 1958). The heights of 15 and the weights of 17 were within +1 S.D. and −1 S.D. (representing about the 84th and 16th percentile respectively); the heights of 19 and the weights of all 20 were above the −2 S.D. line. There is therefore no evidence of a general retardation of growth.

Physical examination of the group of 31 was normal with one exception. This was a girl aged 2 years 4 months who has acyanotic congenital heart disease (probably a septal defect). She is the one child whose height is below the −2 S.D. line.

Mental development was assessed by a consideration of developmental milestones, scholastic progress, comparison with siblings, and observation at the interview. Two children were mildly retarded. One, aged 5, was late in passing all his milestones, and his mother regards him as backward compared with his five siblings. The other, aged 10, has been rather dull and had occasional tonic convulsions until a year ago. The three children whose information was obtained by letter were mentally normal as judged by developmental history, comparison with siblings, and progress at school. The child who died of leukaemia had been normal until the terminal illness. Finally, one child was readmitted to hospital three times before the age of 8 months, and during his last two admissions he showed evidence of gross mental deficiency, with spastic quadriplegia. His temperature on the first admission was 88° F. (31.1° C.) and his clinical picture that of moderately severe chilling. He was 3 weeks old, having been kept in a maternity home since birth. Birth and neonatal period were said to

have been normal and no cerebral signs had been seen; but we cannot, of course, be sure that he did not suffer perinatal cerebral damage.

The prognosis, therefore, appears to be very good for babies who survive the initial episode of chilling. Only 3 out of 36 had disabilities which might possibly be attributable to it—namely, cerebral palsy, mild mental retardation, and epilepsy with mild mental retardation. With one exception there was no interference with growth and physical or mental development in the remainder.

Discussion

Cold injury is, for the most part, a preventable disease. If ever central heating becomes a widespread method of heating houses in this country, then its incidence will presumably decrease. Apparently it is almost unknown in North America, probably because there the houses are properly warmed and many more confinements take place in hospital. However, it seems unlikely that many bedrooms in Britain will be efficiently warmed for some time to come, and therefore active measures will be needed to prevent the condition. The most important measure is the education of all who handle newborn babies at home in the danger of its occurrence during the cold months of the year, in the factors which predispose to it, and in its recognition. The appendix to the paper of Mann and Elliott (1957) sets out simple rules for midwives which, if followed, would substantially reduce the incidence of this disease. The recognition that a baby is chilled is also important, and in the early stages this can be difficult unless the condition is kept in mind. The complaint by the parent or midwife that a baby in the first week of life is refusing to feed, that it is cold, or that the limbs are swollen is highly significant in the cold months of the year. Unfortunately a low-reading thermometer will seldom be carried by the practitioner or midwife.

Probably all chilled babies should be admitted to hospital. Certainly the severely chilled ones need all the resources of modern paediatric care, even though the details of treatment are still controversial.

Summary

All hypothermic newborn babies (183) admitted to the Children's Hospital, Birmingham, over an 11-year period were classified into aetiological groups. Seventy of these were examples of "primary cold injury," the most important or only factor being external chilling.

In three-quarters of the 70 babies the minimum air temperature at the start of their illness was below 35° F. (1.7° C.); in four-fifths the chilling occurred in January to March. Other factors thought to be important are delay in wrapping the baby after birth, tight wrapping, failure to heat the room at night, as well as factors inherent in the neonate. Nearly all were born at home.

The commonest *symptoms* were feeding difficulty, oedema, coldness to touch, and lethargy. Symptoms dated from birth in a third and from the first week in four-fifths. The commonest *signs* on admission were oedema (77%), immobility, a florid complexion, and sclerema. Oedema is thus an important pointer to the diagnosis.

Oliguria was common in severe cases, and in a small investigation the blood urea, phosphorus, and potassium were found to be elevated.

Treatment varied, but it is agreed that warming should be slow.

One-quarter of the babies died. Pulmonary haemorrhage was a universal finding at necropsy.

A follow-up survey of 36 (69%) survivors showed that 92% were normal. One child has cerebral palsy and two are mentally retarded to a mild degree.

We thank the consultant staff of the Children's Hospital for access to their patients; Professor J. M. Smellie for his advice and encouragement; Dr. H. Baar for necropsy reports; Professor D. V. Hubble and Dr. O. H. Wolff for helpful criticism; successive residents for careful case-notes; the nursing staff for their observations and nursing care; and the director of the Edgbaston Meteorological Observatory for climatic information.

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ANENCEPHALY AND OTHER CONGENITAL ABNORMALITIES

AN EPIDEMIOLOGICAL STUDY IN NORTHAMPTONSHIRE

BY

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Congenital abnormalities merit the same detailed epidemiological study to-day which in the past has been devoted to infectious disease. The necessary information can be obtained from the local authority and hospital records; medical practitioners and health visitors can give invaluable help in providing details of individual cases. In Northamptonshire a register of congenital abnormalities has been compiled for each local authority district from 1944. The information has been obtained as follows:

1. Routine searches have been made of the hospital birth registers, the domiciliary birth registers, and the infant mortality registers.

2. All midwives and health visitors have been asked to notify congenital abnormalities. Recently a new section has been added to the midwives' antenatal records and the health visitors' infant record cards asking for a definite statement whether or not an abnormality is present.

3. With the co-operation of the consultant obstetricians and paediatricians, their records have been made available for scrutiny in those cases where a congenital abnormality is present.

4. The records of the mental health department have been examined in regard to mental defectives; the records of the handicapped pupils register of the school health department have also been examined for children with congenital defects.

5. The health visitors and midwives of the local health authority have been asked to ascertain the address or addresses at which the mothers were living throughout pregnancy.

6. In nearly every case it has been possible to confirm the diagnosis by medical opinion.

From these sources the following information is presented.

Anencephaly

Incidence

The great majority of case records of anencephaly and other abnormalities of the central nervous system have been obtained from the hospital birth registers. The incidence of these and other abnormalities is shown in Table I. It will be seen that the figures for Northamptonshire are comparable with those obtained by Penrose (1955) from Queen Charlotte's Hospital and University College Hospital.

TABLE I.—*Births of Infants with Congenital Abnormalities in Northamptonshire, 1944–57*

Year	No. of Live and Still-births	No. of Cases of					
		Mongolism	Congenital Heart Disease	Hare-lip; Cleft-palate	Anencephaly	Spina Bifida	Hydrocephaly
1944	4,798	6	16	10	3	10	1
1945	4,443	7	10	4	2	7	3
1946	4,639	4	10	7	4	9	1
1947	5,011	8	18	1	6	10	3
1948	4,423	5	13	11	1	5	2
1949	4,127	7	18	5	2	5	1
1950	4,078	6	17	12	7	6	2
1951	4,096	9	12	5	3	7	4
1952	4,090	6	13	6	6	16	—
1953	4,342	12	11	4	7	6	2
1954	4,396	9	14	8	7	8	4
1955	4,286	7	10	11	3	12	6
1956	4,656	10	7	12	6	10	7
1957	4,839	3	26	5	7	5	2
Total	62,224	99	195	101	64	116	38
Incidence % live and still-births		0·16	0·31	0·16	0·1	0·19	0·06
Incidence % in University College Hospital and Queen Charlotte's Hospital (1947–51) (Penrose)		0·2	0·24	0·11	0·15	0·125	0·09

Geographical Distribution of Births

When the births of abnormalities of the central nervous system are plotted out on the map it becomes evident that they are more common in urban than in rural areas. In particular, the urban incidence of anencephaly and hydrocephaly is about double the rural incidence (Table II). Most cases in rural areas are born not far distant from towns. Thus in 1956 and 1957 only 3 of the 13 patients with anencephaly were born in local authority rural districts, and one of these was, in fact, born on a housing estate on the Northampton borough boundary.

If the distribution of anencephaly is studied in more detail it will be found that the highest incidence of cases occurs in the industrial belt. From a geographical aspect Northamptonshire is primarily a a rural county; but an industrial belt associated with ironstone extraction, steel manufacture, boot and shoe production, clothing, and light engineering traverses its northern waist (Fig. 1). Although the ratio of live births and stillbirths in the industrial belt in proportion to the rest of the county is only 1.3 : 1, a similar ratio of anencephalic births is 4 : 1. Anencephaly, therefore, is three times as common in the industrial belt as elsewhere in the county.

TABLE II.—*Urban and Rural Incidence of Congenital Abnormalities and some Notifiable Diseases in Northamptonshire (1944–57)*

	Total	Boroughs and Local Authority Urban Districts	Local Authority Rural Districts	Ratio Urban : Rural
Live births	60,890	32,484	28,406	1·1 : 1
Abnormalities:				
Anencephaly (including anencephaly with spina bifida)	64	43 (40)	21 (18)	2·0 : 1
Hydrocephaly	38	25 (21)	13 (13)	1·9 : 1
Spina bifida (including spina bifida with hydrocephaly)	116	67 (54)	49 (47)	1·4 : 1
Congenital heart disease	195	92 (86)	103 (99)	0·9 : 1
Cleft-palate/hare-lip	101	57 (51)	44 (41)	1·3 : 1
Mongolism	99	49 (49)	50 (50)	1·0 : 1
Notifiable infections:				
Scarlet fever	4,515	2,569	1,946	1·3 : 1
Whooping-cough	7,997	3,775	4,222	0·9 : 1
Poliomyelitis	380	226	154	1·5 : 1
Measles	35,342	20,739	14,603	1·4 : 1
Erysipelas	614	408	206	2·0 : 1

The figures in parentheses represent the number of cases where it was possible to confirm the address of the mother at the time of conception and early pregnancy.

It is unlikely that these urban and rural differences have resulted from chance, since the same findings are apparent in Scotland, where stillbirths are classified under the registered cause of stillbirth. The distribution of stillbirths with anencephaly as the registered cause for the years 1951–6 indicates that anencephaly is most prevalent in the lowlands around Clydeside and the Lothians (Registrar-General for Scotland Reports). Anencephaly is comparatively rare in the sparsely populated Highlands. In general, it is more common in the towns than in the rural areas, the highest incidence being in Greenock. Hence it would appear that anencephaly is related to the density of the population.

FIG. 1.—Distribution of 64 anencephalic births in Northamptonshire, 1944–57

Grouping of Births

A very definite feature of anencephaly is the way in which the births occur in groups in time and space. This was noted a hundred years ago by Del-Vesco (1859), an obstetrician in Italy, and is present in Northamptonshire to a marked degree. This grouping is illustrated in Fig. 2, from which it can be seen that, over a period of 14 years, in the village of Loddington with five births a year, the only two cases of anencephaly were born in the same year, 1950. In Cransley, with five births a year, 16 months separated the dates of the two births: in the interval a baby was born in the village with a hare-lip and palate-cleft. In Kettering 5 out of 13 anencephalics were born in one year, 1954. It is noteworthy that there were only two other anencephalics born in the county in that year. In Corby four out of eight anencephalics were born in one year, 1957. In Burton Latimer two out of three anencephalics were born in 1953. At the southern end of the industrial belt, in Higham Ferrers and Rushden, three out of five anencephalics were born in one year (1950).

The anencephalic births in Corby merit further attention. Of the four mothers who gave birth to

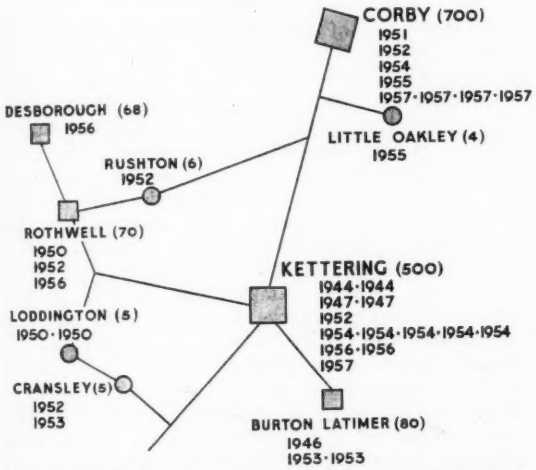

FIG. 2.—Distribution of anencephalic births in Kettering Borough and Rural District and the Urban Districts of Corby, Desborough, Rothwell, and Burton Latimer during the years 1944–57. The figures in parentheses indicate the approximate number of annual births.

anencephalics in 1957, two were living in adjacent streets during their pregnancies. Two other mothers who lived in one of these streets during pregnancy gave birth to abnormalities in 1958: in one case the baby was an anencephalic and in the other a hydrocephalic.

The dates of the births were: July 5 and October 14, 1957, and May 1 and September 14, 1958.

About a mile away two more anencephalics have been born in another street. The dates of these births were: May 29, 1955, and March 17, 1957.

It is possible that this localization of anencephalic births is due to chance, but the coincidence is so striking that it seems reasonable to accept, as a working hypothesis, the idea that they may have some common local cause.

Social Factors

Poverty is difficult to define in the Welfare State. Nevertheless, one gains the impression that anencephaly is more common among persons in the lower-income groups with large families who live in the poorer houses or areas of the town. The part of Corby referred to above, for example, contains some of the poorer dwellings; moreover, it lies in the immediate vicinity of the extensive Stewart & Lloyds steel factories. Coffey and Jessop (1957), in their inquiry in Dublin, reported an apparent association between anencephaly and unemployment and poverty. The same association with social class was noted by Edwards (1958).

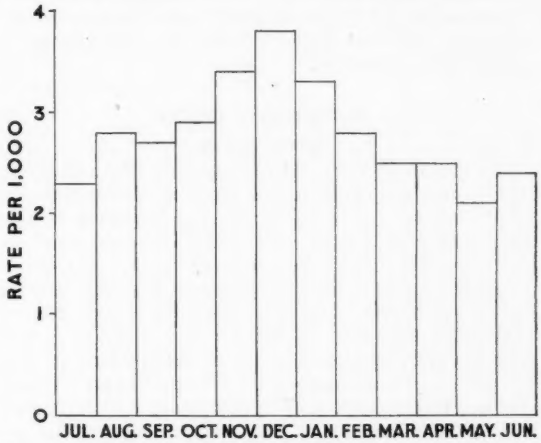

FIG. 3.—Monthly stillbirth rates attributed to anencephalus in Scotland in 1951–6.

Seasonal Incidence

The numbers of anencephalic births in Northamptonshire are insufficient to allow deductions in regard to seasonal incidence. The monthly stillbirth rates attributed to anencephalus in Scotland in 1939–46, however, were shown to exhibit a seasonal variation (McKeown and Record, 1951). The same variation is evident for the years 1951–6 (Fig. 3) (Registrar-General for Scotland, Reports for 1951–6). More cases are conceived in the summer than in the winter months.

Association of Abnormalities with Infections

From the facts presented it appears that anencephaly is associated with the density of the population and the seasons of the year and that it is more common among the lower-income groups of the population living in crowded conditions. In Northamptonshire, however, it is the grouping of anencephalic births which most attracts attention. At times anencephalic births appear to be associated with other abnormalities of the central nervous system. (Thus, for example, in the village of Bozeat, with about 17 births a year, the only congenital abnormalities recorded over a period of 14 years are one case of anencephaly and one case of spina bifida. Both were born at full term on the same day—February 23, 1947.) At other times there appears to be no association between anencephalics and other abnormalities: the anencephalics seem to form a distinct group on their own.

The environmental features which have been described could be explained if infections were commonly the cause of anencephaly and other

abnormalities. One would then expect the higher urban incidence which characterizes many infections, particularly erysipelas (Table II). One would also expect the births to be in groups: indeed, it would be strange if this were not the case, since in effect one would be noting a series of complications of an infectious process. Social factors relating to poverty and overcrowding could also be explained. At the present time, however, rubella is the only infection with which abnormalities have often been associated. Toxoplasma and syphilis are known to produce foetal abnormality, but the evidence is based mainly on individual clinical cases. An association between other maternal infections and foetal abnormalities must therefore remain largely hypothetical until more definite evidence becomes available either by retrospective or by prospective inquiry.

Retrospective Inquiry

Epidemiological

By means of retrospective inquiry Coffey and Jessop (1957) obtained evidence that mothers of anencephalics experienced more illness during the first three months of pregnancy than the mothers of controls. Retrospective inquiry from a small number of mothers of anencephalics in Northamptonshire, however, failed to reveal any history of definite febrile illness in pregnancy. The main drawback of retrospective inquiries is that reliance must be placed on the mother's memory. But despite this disadvantage epidemiological inquiry should be encouraged—especially in new towns with high birth rates—since there are occasions when abnormalities are born in a way that suggests the role of environmental factors in their aetiology.

Thus in Corby in 1957, of 850 babies born in the town, seven had a defect of the heart. Three of the seven babies were born in one street and its adjoining cul-de-sac, in which 17 babies were born in the year. A fourth baby in the street was born with hare-lip and palate-cleft. Two other babies had large naevi and another was born with bat ears. The three babies with heart defect died shortly after birth. In 1958 another baby born in this street also died from congenital heart disease (Fig. 4). In each case the heart abnormality was verified by consultant opinion or necropsy.

Congenital Disease of the Heart

Case 1.—Male. Born June 29, 1957; died August 13, 1957. Medical death certificate: cardiac failure; congenital heart disease. Post-mortem report: endocardial fibroelastosis. When the mother was three months pregnant one of her children had a feverish illness with vomiting and diarrhoea.

Case 2.—Male. Born October 3, 1957; died October 27, 1957. Consultant opinion: congenital disease of heart. When the mother was five months pregnant one of her children had chicken-pox.

Case 3.—Female. Born November 18, 1957; died March 27, 1958. Cause of death: cardiac failure; congenital heart. Seen at Great Ormond Street Hospital: opinion, tricuspid atresia. Baby appeared microcephalic. Maternal history of "three-day 'flu" in second month of pregnancy.

Case 4.—Male. Born October 6, 1958; died October 9, 1958. Post-mortem report: patent foramen ovale.

Other Abnormalities Born in the Street

Case 5.—Male. Born January 14, 1957. Naevi on cheek, leg, and finger.

Case 6.—Male. Born July 7, 1957. Bilateral bat ears.

Case 7.—Male. Born August 26, 1957. Bilateral hare-lip. (Family history of hare-lip.)

Case 8.—Female. Born December 30, 1957. Single naevus on abdomen.

This distribution of defects cannot be explained satisfactorily on the basis of chance. Yet, although a detailed inquiry was made, a history of maternal illness could be obtained in only one case (Case 3). In the course of the year some children living in the street had had chicken-pox; others had had whooping-cough. It is submitted that the most satisfactory explanation of this grouping of heart defects is on the basis of maternal infection.

Another example may be cited. In Rushden, at the southern end of the industrial belt, there were 247 live births and stillbirths in 1958. Two babies were born with congenital heart defect. In both cases the diagnosis was verified at necropsy. The two babies were born in the same street within six months of one another. Only four babies were born in this street during the year.

Serological

Another form of retrospective inquiry which may provide information is to undertake maternal serological examination after the abnormal baby has been born. In the same way that a retrospective diagnosis of enteric fever can be made on the evidence of a raised agglutinin titre, so it may be possible to obtain serological evidence which indicates previous maternal infection by one or more organisms. It is probable, however, that if infections are associated with abnormalities, the infections are common enough in the community for it to be difficult to establish a difference of statistical significance between sample and control groups. Nevertheless, an attempt seemed worth while, and with the co-operation of Professor C. P. Beattie of the toxoplasma laboratory, Sheffield, and Dr. L. Hoyle, of the Northampton Public Health Laboratory, samples of blood from mothers who had given birth to babies with abnormalities of the central nervous system were examined for antibodies to the following infections: toxoplasma, influenza A, B, and C, Q-fever, psittacosis, adenovirus, mumps, lymphocytic choriomeningitis. As control for each case a mother was selected of

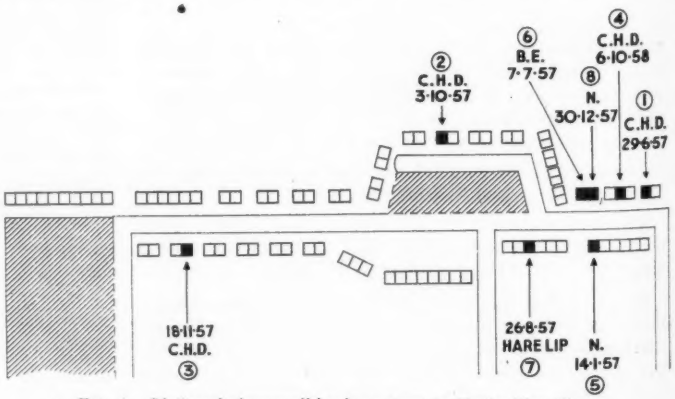

FIG. 4.—Births of abnormalities in a street in Corby New Town.

approximately the same age and multiparity and living within a distance of five miles. Similar investigations for poliomyelitis and the Coxsackie group of infections would appear justifiable in the future, but the scope of the present inquiry was limited on account of the work involved and had to be discontinued for practical reasons before any definite conclusions could be reached.

Prospective Inquiry : Asian Influenza in Pregnancy

The advantages of prospective inquiry in attempts to associate cause and event are obvious. McDonald (1958), by this means, showed that congenital abnormalities could be associated with, among other things, a higher incidence of febrile respiratory infections in pregnancy. Coffey (1958), in a preliminary report on a prospective study of 600 mothers who said they had had influenza, found that the incidence of malformed babies born to them was 3.8% as compared with 1.7% in a control group. Among 88 women who had been ill in the first trimester the incidence of congenital abnormalities was 9%. In a similar study of about 200 mothers whose diagnosis of influenza had been confirmed by a general practitioner, Doll (1958) found the incidence of congenital abnormalities to be 3%.

In Northamptonshire a small prospective inquiry was undertaken to ascertain the effects of Asian influenza in pregnancy on foetal development. Dr. C. M. Smith, the County Medical Officer, sent out a questionary to all midwives practising in the county asking them to notify details in regard to all expectant mothers under their care who suffered from Asian influenza. In response to this inquiry, notifications were received during the ensuing months of 43 expectant mothers who had fallen ill with Asian influenza. The details provided in respect of each case showed that 38 of the 43 mothers had suffered an illness severe enough to compel them to go to bed ; in one case the patient could not go to bed as all the other members of the family were also affected. The length of stay in bed varied from half a day to three weeks ; the average duration was five days in bed. Of the 43 patients, 33 called in their doctor. In 26 of the cases other members of the family were also affected with the same form of illness. In all but three cases the patient made a satisfactory recovery.

The illness itself as described by the midwives consisted of headache, fever, pain in the limbs, "typical influenza," and depression. No attempt was made to identify the organism responsible for the illness, and it may well be argued that there is no scientific evidence that these were cases of Asian or any other form of influenza. This reservation is accepted. It is, however, true to say that the mothers suffered from a febrile illness with symptoms and signs similar to influenza during the time when the Asian influenza reached epidemic proportions in the county.

After the notifications of the midwives had been received they were filed, and when then the baby was born some months later the details on the midwives' antenatal records and on the health visitors' birth inquiry cards were checked to ascertain whether any abnormality was present. Where an abnormality was recorded, information regarding the nature of the abnormality was obtained from the records of the medical practitioner, the medical death certificate, or the hospital records. In this way medical confirmation of each abnormality was obtained. Two cases of abortion were taken from the midwives' records.

For the purpose of controls for this series of cases the midwives were asked to send in their records for all other expectant mothers under their care who were pregnant during the period September 1 to December 31, 1957, when Asian influenza was prevalent in the county. A total of 1,040 controls were obtained in this way. In 62 cases only the midwives' antenatal records were available, but in the remainder the details of the births were analysed both from the midwives' records and from the health visitors' birth inquiry cards in the same way as in the sample group. A summary of the results in the two groups is shown in Table III. Although the figures in the sample group are probably too small to allow valid deductions to be drawn from them, it will be seen that the incidence of congenital abnormalities and abortions is higher among the sample than among the control group.

TABLE III.—*Asian Influenza in Pregnancy. Incidence of Congenital Abnormalities, Abortions, Stillbirths, and Infant Deaths as Obtained from a Prospective Inquiry in a Group of Mothers who Suffered "Asian influenza" in Pregnancy, as Compared with a Control Group*

	Sample Group	Control Group
1. Total ..	43	1,040
2. Abnormalities	3 (1 congenital heart disease. 1 spina bifida and hydrocephalus. 1 hydrocephalus)	14 (1 anencephaly. 1 hydrocephaly. 1 hydrocephaly and spina bifida. 7 congenital heart disease. 1 hare-lip cleft-palate. 2 mongols. 1 congenital hip) In addition six minor defects were noted: 3 pyloric stenosis, 3 defects of feet
3. Abortions ..	2	10 (One occurred in a twin pregnancy)
4. Stillbirths ..	—	20 (Two occurred in twin pregnancies and one in a triplet pregnancy)
5. Infant deaths	1	8

Of 12 mothers who had Asian influenza in the first trimester, one gave birth to a baby with hydrocephalus ; a second aborted at the fourth month of pregnancy ; a third aborted at the sixth month of pregnancy. Of the 18 mothers who had Asian influenza in the second trimester, one gave birth to a baby with congenital heart disease. A second baby died three days after birth from bronchopneumonia. The clinical condition of this baby as described by the practitioner suggests that the cause of death may have been associated with neonatal cold injury. Of the 13 mothers who had Asian influenza in the third trimester, one gave birth to a baby with spina bifida and hydrocephalus.

Discussion

From the information presented it seems reasonable to suggest that there may be an association between Asian influenza in pregnancy and congenital abnormality. As with rubella, the risk of foetal damage appears to be greater when the illness has occurred in the early months of pregnancy, although Doll (1958) did not find this to be the case in his inquiry.

This evidence can be considered in relation to other facts which are available. Firstly, the prospective survey by McDonald (1958) showed there was an

association between congenital abnormalities and febrile illness in pregnancy, while the retrospective survey by Coffey and Jessop (1957) indicated that mothers of anencephalics experienced more illness in the first three months of pregnancy than the mothers of controls. Secondly, Lundström (1952), in his inquiry, showed that there was an increased incidence of abnormal foetuses born to mothers who had come in contact with rubella, even though they themselves had previously had rubella and gave no history of illness in pregnancy. Hence the immunity which is sufficient to protect the mother from overt illness is not necessarily sufficient to protect the foetus from attack. Thirdly, the epidemiological evidence in Northamptonshire strongly suggests that there is a much greater association between maternal infection and congenital abnormalities than is at present accepted.

Attention has already been drawn to the fact that approximately two-thirds of mongol births in Northamptonshire occur in groups (Pleydell, 1957). This distinctive grouping holds good for other abnormalities also: congenital disease of the heart, urogenital abnormalities, and orthopaedic abnormalities not infrequently occur in a manner strongly suggestive of an infectious process. Epidemiological studies of births of abnormalities—particularly in new towns with high birth rates—can produce circumstantial evidence of the causal role of infections where clinical inquiry fails to elicit a history of illness or contact with illness.

The outstanding feature of Asian influenza was the lack of native resistance to the infection. The illness sustained was generally sufficient to send the affected mothers to bed for several days. It is unlikely that this illness would have been overlocked had a retrospective inquiry been made. In fact, in cases where retrospective inquiries were made the mothers were quite definite in the information they gave, and it was generally possible to confirm the history from the general practitioner. It appears, therefore, that if the characteristic grouping of congenital abnormalities described in this paper is associated with maternal infections, such infections must be less severe to the adult than Asian influenza. The fact that we have not as yet identified them is more a reflection on our present state of ignorance than an indication that they do not exist.

The association between maternal infection in pregnancy and foetal abnormality is of the greatest importance when considering the possibility of prevention. At present public health measures can be taken to prevent an expectant mother from coming into contact with rubella; mothers who have been exposed to rubella can be protected by passive immunization with gamma-globulin. Toxoplasma is sensitive to sulphonamides. If it is confirmed that influenza in pregnancy is associated with congenital abnormality, protection may be possible by active immunization. Perhaps in the future the protection of the individual against infection will start before or soon after conception rather than shortly after birth.

In the existing scheme of antenatal care more and more attention is devoted to the expectant mother as the pregnancy advances. Little attention is paid to the early weeks of pregnancy—which are more critical for the foetus—since the mother often does not attend for examination until the second trimester. It is evident, however, that if preventive measures are to be effective there must be supervision of the early stages of pregnancy. The *British Medical Journal* (1958) advised parents who had had an anencephalic child to restrict future conceptions to the winter months. The planning of pregnancies would appear to be a rational measure for parents where there is a history of abortions, stillbirths, or abnormalities.

The evidence presented in this report draws attention to the need for further epidemiological inquiry into the cause of abnormalities. It could well be argued that it would be profitable to introduce notification and supervision in respect of the conditions which we do not understand, in place of the mild infections with which we are familiar. The recommendation in the *Lancet* (1947) that infections in pregnancy should be notifiable is as valid now as it was when it was made. Equally great is the need to maintain registers of congenital abnormalities so that accurate records can be kept in different areas throughout the country. It would appear that these administrative steps are essential if concerted measures are to be undertaken with the object of learning more about the association between prenatal infections and congenital abnormalities.

Summary

An epidemiological study in Northamptonshire provides evidence that anencephalic births are related to the density of the population. The incidence of anencephaly in urban districts is double the incidence in rural districts; the incidence in the industrial belt is three times the incidence in the rest of the county.

A definite feature of anencephalic births is that they occur in groups in time and space.

It is suggested that the association between anencephaly and social class, season of the year, density of population, and the grouping of births is best explained on the basis of an infectious causation.

A description is given of a group of births of different congenital abnormalities in one street in Corby New Town.

The results of a small prospective inquiry in Northamptonshire suggest that there may be an association between Asian influenza in pregnancy and congenital abnormalities.

Stress is laid on the importance of further epidemiological inquiries in regard to congenital abnormalities; attention is drawn to the possibility of prevention of those cases associated with infections.

I thank Dr. C. M. Smith, County Medical Officer of Health, Northamptonshire, for his advice and encouragement in undertaking this survey; Dr. McKinlay, from the Department of Health for Scotland, for providing me with statistics of the incidence of anencephaly in Scotland; and the consultant paediatricians and obstetricians who let me see their records. I am indebted to the doctors who provided me with information in many cases; to the health visitors and district-nurse midwives for their conscientious inquiries on my behalf; and to the staff of the health department and the hospitals for the help they gave me.

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PREVENTION OF STAPHYLOCOCCAL SEPSIS IN A MATERNITY HOSPITAL BY MEANS OF HEXACHLOROPHANE

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In a previous paper (Gillespie *et al.*, 1958) we showed that infants who became heavily colonized by *Staphylococcus aureus* within a day or two of birth subsequently developed septic lesions of the skin more often than other infants. This tendency was particularly pronounced with staphylococci of phage patterns 52A/79 and 80, which were the most virulent strains prevalent in the hospital. The application to the umbilical area of a dusting powder containing hexachlorophane greatly reduced the staphylococcal colonization of the umbilicus and groin, and reduced the colonization of the perineum and nose to a smaller extent.

We report here some further results obtained in the same investigation. The clinical and bacteriological effects of applying hexachlorophane powder from earlier in life and to a wider area of skin were studied. Changes in nursery routine which reduced the contacts between infants and nurses were investigated.

The basic nursery techniques were described in our previous paper. Some changes then introduced were continued: namely, the disinfection of blankets and garments; the use of hexachlorophane soap for hand-washing; and the sealing, with "octaflex," of umbilical-cord stumps, which were then left uncovered. Chlorhexidine ("hibitane") hand-cream was withdrawn, however, so as to simplify the present trial.

Effect of Hexachlorophane Powder

Fig. 1 shows the results of direct plating of swabs taken from the carrier sites of most infants admitted to nurseries 2 and 3 of the Bristol Maternity Hospital. (Swabs from infants treated with hexachlorophane were soaked before use in 1% "tween 80" broth and plated on nutrient agar similarly fortified.) Enrichment culture in salt meat broth gave slightly more positive cultures but did not affect the general patterns of the graphs. From February 26 until August 17, 1958, hexachlorophane powder ("ster-zac") was applied to the umbilicus and the front of the abdomen of every infant admitted to nursery 2, and this was repeated every time the napkin was changed, until the cord separated. From August 18, 1958, until June 15, 1959, the infants were first powdered in the labour room before they went to nursery 2, and the powder was applied repeatedly to the whole trunk, including the buttocks, perineum, axillae, and groins as well as the umbilicus, until the infants left hospital. The more liberal use of the powder did not improve the protection of the umbilicus and groin, but perineal and nasal colonization was further reduced (Fig. 1). In nursery 3, where no powder was used until February 13, 1959, the colonization of all four carrier sites continued at much higher levels than in nursery 2 (Figs. 1 and 2).

After the introduction of powdering of the umbilical area, the incidence of staphylococcal lesions of the skin fell from 19/365 (5.2%) to 7/343 (2.0%) (see Table).

Effect of Hexachlorophane Powder on the Incidence of Staphylococcal Skin Lesions

	Nursery 2			Nursery 3
	7/7/57–24/1/58	26/2/58–17/8/58	18/8/58–15/6/59	19/5/58–12/2/59
Area powdered ..	None	Umbilicus	Whole trunk	None
No. of infants ..	365	343	554	464
,, with skin sepsis	19 (5·2%)	7 (2·0%)	5 (0·9%)	34 (7·3%)

The difference was statistically significant ($\chi^2 = 5.0$; $P < 0.05$). Subsequently, with the more liberal use of the powder, the incidence of sepsis fell again, to 5/554 (0.9%). In the control nursery 3 the incidence of sepsis in a comparable period remained high, at 7.3% (see Table), and there occurred a small outbreak of pemphigus neonatorum caused by a penicillin-resistant

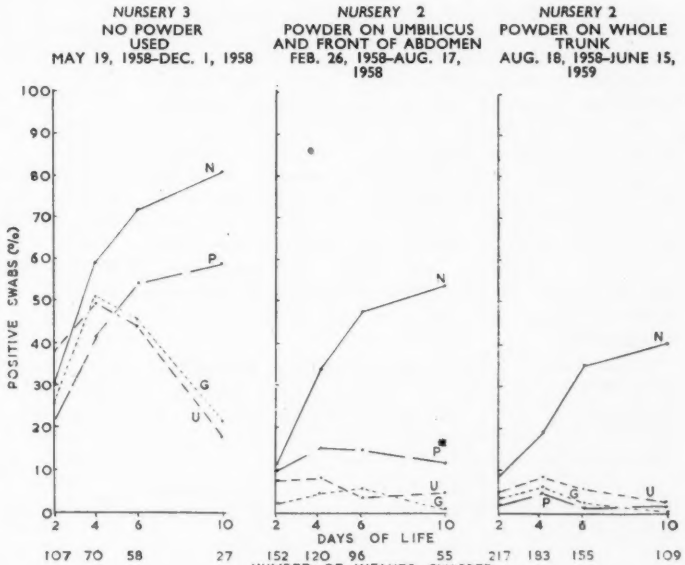

FIG. 1.—Effect of hexachlorophane powder on staphylococcal colonization of infants. N = Nose. P = Perineum. U = Umbilicus. G = Groin. *Perineal swabs were not taken before May 3. Numbers of perineal swabs on 2nd, 4th, 6th, and 10th days were 96, 75, 63, and 32 respectively.

type-80 staphylococcus, and a series of pustules caused by a penicillin-resistant strain with the phage-pattern 79. Both strains spread widely in the nursery but did not spread to nursery 2 on the floor immediately below, despite several interchanges of staff.

Because of the pemphigus, nursery 3 was closed to new admissions on September 2, 1958. After all the infants had been discharged the walls, floor, and furniture were disinfected, and bedding was changed.

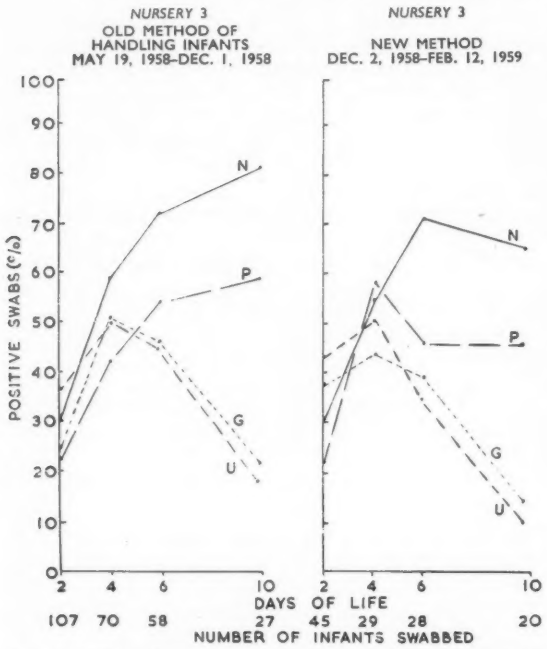

FIG. 2.—Effect of reducing contact between infants and nurses (see text). N=Nose. P=Perineum. U=Umbilicus. G=Groin.

After the reopening of the nursery on September 11 there were no more lesions caused by the epidemic strains, but the infants became colonized by other staphylococci almost as quickly as before. Of the first 10 infants admitted, five became nasal or umbilical carriers by the fourth day of life (and two of these later developed staphylococcal lesions of the skin) compared with 7 of the 10 admitted immediately before the closure. The staphylococci which spread among the infants after the nursery was reopened probably came from carriers among the nursery staff. This experience confirmed our belief that precautions directed solely against inanimate vehicles of infection such as walls and furniture are likely to prove disappointing.

While nursery 3 was closed all full-term infants had to be admitted to nursery 2. But, despite the consequent overcrowding, there was no perceptible increase in staphylococcal cross-infection, thus demonstrating the efficiency of the disinfectant powder.

In a period of 18 months more than 1,000 infants have been treated with hexachlorophane powder without irritation of the skin or other harmful effects.

Effect of Reducing Contact Between Infants and Nurses

Most infants remained in their nurseries except when feeding, the design of their mothers' rooms making it difficult for more than a few to practise "rooming-in." Nurses carried infants one at a time to their mothers, each infant being wrapped in a "pack" consisting of a blanket contained within a pillow-cover. Complementary feeds were given by nurses, who held the infants and did not change gowns afterwards. Napkin changes were carried out with the infants on nurses' laps. It seemed that some of this contact was avoidable, and that it might be an important channel of cross-infection. Accordingly, on December 2, 1958, new methods of handling infants were introduced into nursery 3 (where hexachlorophane was not used) and their effects were observed for the ensuing 11 weeks. Wheels were fitted to cots, and infants were wheeled to their mothers and picked up by them unless the mother's condition contraindicated this. Infants remained in their cots while napkins were changed and complementary feeds given. These modifications did not greatly reduce contact with nurses' hands, but contact with their uniforms was much reduced.

The changes in routine, though faithfully carried out by the nurses, had no appreciable effect on cross-infection (Fig. 2). The incidence of sepsis was unaffected: 8 out of 99 infants developed lesions of the skin, compared with 5 out of 100 infants in the previous 11 weeks. These results are in line with those of Forfar and Maccabe (1958), who found that the wearing, by nurses, of gowns individual to each baby made no significant difference to staphylococcal cross-infection.

Discussion

The incidence and severity of staphylococcal sepsis in maternity hospitals depend on many variable factors, including the virulence of the prevalent staphylococci, the degree of overcrowding in the nurseries, the facilities for "rooming-in" infants with their mothers, and the standard of nursing. Yet another factor may be the average age of the infants. The umbilicus, probably the most important of all carrier sites in early life, tends to lose its staphylococci after the first week (Gillespie *et al.*, 1958). Consequently, a nursery from which infants are discharged when 6 or 7 days old may have a higher staphylococcal load than one in which the infants are kept for a few days longer.

To be effective, precautions against cross-infection must be based on epidemiological knowledge. The ultimate sources of the staphylococci are adults, mainly nurses. But when a staphylococcus from an adult carrier colonizes a newborn infant it is then more readily spread to other infants. The chief *immediate* sources from which most newborn infants in a nursery acquire staphylococci are the other infants.

In order to prevent cross-infection, precautions may be taken against the routes and vehicles of spread of the organisms. But there are many routes, and the closure of only one or two may have little effect. Thus, while contact with contaminated bedding and with the overalls of nurses must play some part in cross-infection, precautions directed solely against these vehicles had no detectable effect. These failures do not mean that the precautions were valueless. They might have value if combined with other precautions.

The hands of the nurses, even when they wash after handling every infant, are important vehicles of staphylococci, and cross-infection was appreciably reduced when the nurses used a disinfectant hand-cream (Gillespie *et al.*, 1958).

Cross-infection may be reduced by keeping infants in separate rooms with their mothers (Hutchison and Bowman, 1957). But for "rooming-in" to be effective, contact with nurses must be kept to a minimum. Some contact is unavoidable, especially in the first few days of life, when it is most likely to lead to dangerous colonization. Consequently the provision of separate rooms cannot be the whole answer to the cross-infection problem.

Precautions may also be directed against the sources of the staphylococci. It is impracticable to exclude all adult carriers from a hospital. An attempt might be made to exclude, or to treat, the carriers of exceptionally virulent strains; but such a policy would be difficult to enforce. If even a few staphylococci were allowed to enter the nursery, they might colonize some infants and multiply so as to form a large staphylococcal reservoir from which other infants would be cross-infected. Moreover, an infant who has been colonized by a virulent strain is a danger to himself as well as to other infants, and probably is a danger to his mother also. The prevention of the staphylococci from multiplying on the infants is an effective way of reducing cross-infection and sepsis. Fortunately, the infants' carrier sites, being superficial, are accessible to disinfectants. The use of hexachlorophane powder for more than a year has greatly reduced staphylococcal infection. Pustules and cutaneous abscesses, hitherto common, are now rare, their incidence among the infants having fallen from about 6% to less than 1%. The most pronounced effect of hexachlorophane on cross-infection was its reduction of staphylococcal colonization of the umbilicus and skin. Nasal colonization was reduced by more than half, but, despite this, about 40% of infants still left hospital as nasal carriers. In work now in progress in a nursery where hexachlorophane is used, this rate has fallen to less than 10% following the twice-daily application of a neomycin–chlorhexidine cream to the infants' nostrils, as suggested by Dr. K. G. Green (personal communication).

The reduction in staphylococcal infection among infants has been followed by a corresponding reduction among mothers. Hexachlorophane powder has been in routine use in most maternity hospital nurseries in Bristol for more than a year. During this period there have been remarkable reductions in the numbers of breast abscesses recorded by the hospitals and health department of the city (personal communications from Professor G. G. Lennon, Dr. Sheila Eades, Mr. H. K. Bourns, and Dr. Sarah Walker).

No single precaution can prevent all staphylococcal cross-infection. A high standard of nursing and the avoidance of overcrowding may in practice keep the incidence of sepsis sufficiently low; but this will depend partly on factors outside the control of the nursing staff, such as the virulence of the staphylococci which become prevalent in the nurseries. If appreciable numbers of infants or mothers suffer from sepsis, the additional use of hexachlorophane dusting powder is a worth-while and easy precaution.

Summary

The repeated application of hexachlorophane dusting powder to the umbilicus and the front of the abdomen greatly reduced staphylococcal cross-infection among newborn infants. Still better results were obtained by starting the treatment before the infants entered the nursery, and by treating the whole trunk, including the groins, perineum, and axillae. The routine use of the powder has been followed by a greatly diminished incidence of staphylococcal sepsis in infants and mothers.

Changes in nursery techniques which reduced contacts between the infants and the nurses' uniforms failed to reduce cross-infection appreciably.

We are indebted to our Board of Governors for a grant which enabled us to do this work. We thank Dr. Beryl Corner for her interest and advice; the matron and nursing staff, Bristol Maternity Hospital, for their co-operation; and Messrs. Hough, Hoseason, and Co. for supplies of ster-zac powder.

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CHRONIC MILK-ALKALI SYNDROME WITH GENERALIZED OSTEOSCLEROSIS AFTER PROLONGED EXCESSIVE INTAKE OF "RENNIE'S" TABLETS

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It has long been appreciated that the treatment of peptic ulcer with alkalis given in excess may lead to complications, and three distinct clinical states have been recognized. Acute alkalosis and temporary renal insufficiency from such a regime has often been described (Hardt and Rivers, 1923; Cooke, 1932; Kirsner and Palmer, 1942). Secondly, Cope (1936) reported four cases with hypercalcaemia as well as alkalosis and a raised blood urea that quickly responded to antacid withdrawal, though their renal abnormalities took several weeks to disappear. The existence of this syndrome has also been confirmed on many occasions (Scholz and Keating, 1955; Wenger *et al.*, 1957). Finally, Burnett *et al.* (1949) described the occurrence of the following syndrome in six patients each with a chronic duodenal ulcer which was being treated with large quantities of milk and absorbable alkalis: hypercalcaemia without hypercalciuria or hypophosphataemia, a normal serum alkaline phosphatase, marked chronic renal insufficiency with azotaemia, mild alkalosis, and calcinosis especially manifested by ocular lesions resembling a band keratitis. Some improvement in the clinical state was noted when the intake of milk and alkalis was reduced. Cases broadly corresponding to these have been reported since by McQueen (1952), Miller *et al.* (1952), Wermer *et al.* (1953), Dworetzky (1954), Dufault and Tobias (1954), Foltz (1954), Kyle (1954), Rodnan and Johnson (1954), and Snapper *et al.* (1954).

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The following case is reported as it is believed to be another example of this third, rare group and to show some features of special interest.

Case Report

The patient, a housewife aged 48, was admitted to hospital on August 19, 1958. She gave a history of loss of energy and general ill-health over the previous two years, with an intensification of these symptoms during the three weeks prior to admission. She had also been troubled recently with severe pruritus, mainly affecting her back, and complained of frequent occipital headaches, nocturia, and some breathlessness on exertion.

She had suffered for about 12 years from dyspepsia and had experienced a haematemesis on two occasions. Investigations on account of this had been carried out elsewhere, and barium-meal examinations in 1956 and 1957 revealed several small gastric ulcers, which subsequently appeared to heal. Her haemoglobin in February, 1956, was 11.3 g./100 ml. and M.C.H.C. 32.5%. Slight proteinuria was then noted and a chest *x*-ray film was reported as negative. On account of her ulcer symptoms she had treated herself with "Rennie's" tablets. She developed a liking for these, taking them even when free from symptoms, and for 10 years had consumed about 30 tablets daily. This represents an intake of 20.148 g. of calcium carbonate and a relatively insignificant amount of calcium phosphate each day. She did not take more than 1 pint (570 ml.) of milk daily, nor was there any evidence of an excessive intake of vitamin D. There was no history suggestive of previous renal disease.

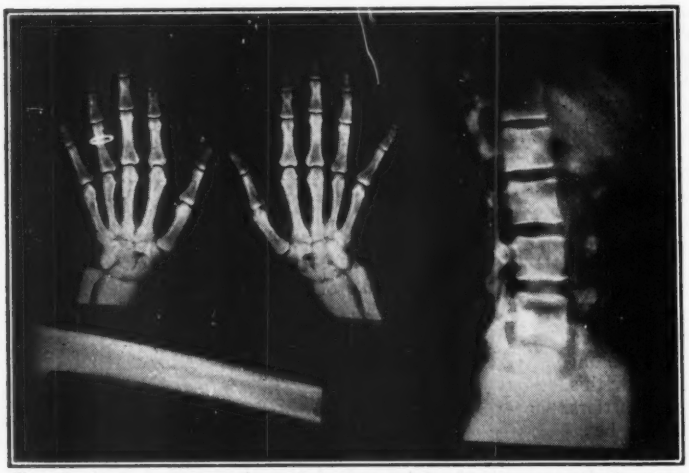

FIG. 1.—Femur, metacarpals, and lumbar spine, showing generalized osteosclerosis. Glandular calcification is also apparent.

On physical examination she was noted to have a dry, sallow skin with pale mucous membranes. There was no swelling in the neck. A few small glands were found in the axillae and inguinal regions. Her blood-pressure was 115/75 mm. Hg, and there was no evidence of cardiac enlargement. Examination of the lenses of both eyes with the slit-lamp and microscope did not show any opacities, but in the palpebral regions there were interstitial deposits of small thin white plaques at the limbus, extending for about 0.5 mm. into the cornea, with similar deposits in the adjacent sclera. In the lower part of the limbus of each eye white lines running radially towards the centre of the cornea about 1 mm. from the limbus were seen. These deposits were presumably composed of calcium. Physical examination was otherwise negative.

Laboratory Investigations.—Haemoglobin, 9.9 g./100 ml.; red-cell count, 3,300,000/c.mm.; P.C.V., 30%; M.C.V., 91 cubic microns; M.C.H.C., 33%; white-cell count, 5,300/c.mm., with normal appearances and distribution; E.S.R., 38 mm. in the 1st hour (Westergren). Blood urea, 180 mg./100 ml.; serum calcium, 9.3 mg./100 ml.; serum inorganic phosphorus, 6.1 mg./100 ml.; alkali reserve, 20 mEq/l.; potassium, 5.0 mEq/l.; chloride, 100 mEq/l.; alkaline phosphatase, 9 King–Armstrong units; total protein, 6.9 g./100 ml. (albumin 3.3 g., globulin 3.6 g.). Liver-function tests were normal. Urine: *p*H 5.4, specific gravity, 1008–1004 on concentration and dilution testing. Slight proteinuria and a moderate microscopic pyuria were noted on occasion, but urinary culture was repeatedly sterile. Mantoux was negative using 1/10,000 old tuberculin, as were the blood Wassermann and Kahn reactions. The 24-hour urinary calcium excretion was 78 mg. There was histamine-fast achlorhydria.

E.C.G. and chest *x*-ray films were normal. A barium-meal examination showed no abnormality in the oesophagus, stomach, or duodenum. Intravenous pyelography revealed small renal outlines and bilateral nephrocalcinosis. Glandular calcification was present in the lower abdomen and there was calcification of the abdominal aorta. Radiology of the skeleton showed a marked increase in the density of the ribs, femora, lumbar spine, and metacarpals. A skeletal survey of a femur, lumbar spine, and hands (Fig. 1) was carried out by Drs. Barnett and Nordin and scored according to their technique (Barnett and Nordin, 1960). The total score of 223 was the highest which they had encountered in their experience of 125 normal patients and 150 with suspected bone disease, indicating an increase in cortical thickness. An iliac crest biopsy (Fig. 2) was also carried out by Dr. Nordin, who during the procedure commented on the extreme hardness of the bone. It was reported on as follows by Dr. Swanson Beck: "The biopsy consists of dense trabecular bone, the trabeculae being numerous and of more - than - average thickness, and are formed of mature normal bone. There is no increase in osteoblastic or osteoclastic activity and there are no osteoid borders."

The biopsy scored 9 on the 9-point scale of Beck and Nordin (unpublished data), confirming the impression of extremely dense bone. An attempt at renal biopsy was unsuccessful. Details of various indices of parathyroid function, such as the calcium infusion test and the so-called tubular reabsorption of phosphate, are omitted, as they are of no diagnostic value in the presence of severe renal damage.

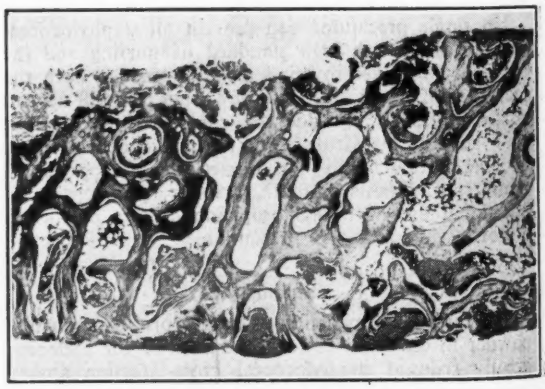

FIG. 2.—Iliac crest bone biopsy, showing the dense, numerous, and thickened trabeculae. (×15.)

Rennie's tablets were discontinued on admission, and shortly afterwards she was put on a high fluid intake with a low phosphate diet. The latter was soon stopped, as it was unpalatable. On this regime she improved symptomatically and a fall in the blood urea occurred. The serum calcium, however, gradually rose above the normal range, and a low calcium diet (290 mg./day) was therefore introduced. She also received sodium bicarbonate for a period to see the effect of counteracting the acidosis. The time relationships of the various treatment regimes and the progress of the serum calcium, inorganic phosphorus, urea, and alkali reserve are shown in Fig. 3. The serum calcium

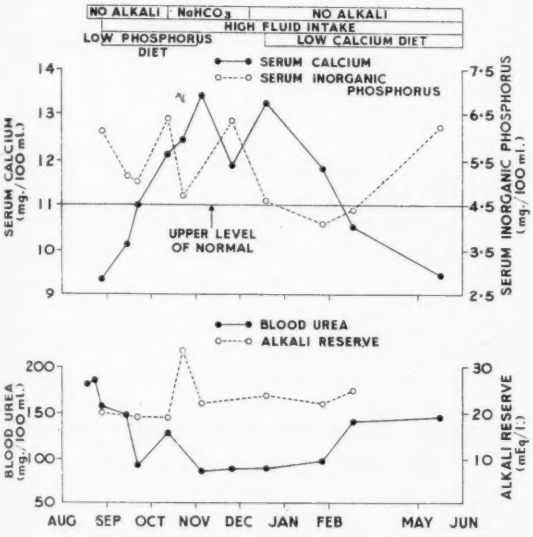

FIG. 3.—Changes in blood urea, alkali reserve, serum calcium, and inorganic phosphorus, and associated treatment.

ultimately returned to normal. The haemoglobin rose to 11.9 g./100 ml. and her nocturia disappeared. *X*-ray films taken six months after admission suggested that the renal calcinosis was less marked than previously.

Discussion

The name "milk-alkali syndrome" has been applied to two distinct clinical states: the short-lived alkalotic episodes with hypercalcaemia, first described by Cope (1936), and the more chronic upsets characterized by soft-tissue calcinosis and advanced renal damage which Burnett *et al.* (1949) later separated, albeit rather tentatively, from primary hyperparathyroidism. As Wenger *et al.* (1957) point out, there is often a failure in the literature to differentiate between these two syndromes, and though it is reasonable to suspect that they merely represent varying stages of the same disease, it is of interest that in few, if any, of the chronic cases so far described has there been a history of such acute incidents, and, conversely, Wenger *et al.* (1958), in their series of acute cases, did not find evidence of permanent renal damage. Thus we feel that the term "milk-alkali syndrome" should be qualified by "acute" or "chronic" as suits the case. We also deplore the current tendency to label all acute or chronic cases as "the Burnett syndrome," as Cope was the first to recognize the hypercalcaemia, which is the leading feature common to both groups. Even the name "milk-alkali syndrome" is open to some criticism, as one of the cases of Snapper *et al.* (1954) had no history of an excessive intake of milk, nor did Rodnan and Johnson's (1954) case or our own. However, we feel that, generally, the term is a useful one as an indication of the circumstances with which the condition is usually associated.

Burnett *et al.* (1949) suggested several features which they thought favoured the diagnosis of their syndrome rather than primary hyperparathyroidism, though this, they admitted, could not be completely excluded. These were: a history of prolonged intake of milk and alkali, no hypercalciuria or hypophosphataemia, absence of skeletal changes and a raised serum alkaline phosphatase, the presence of renal insufficiency with mild alkalosis, calcinosis, and finally improvement on a low calcium and alkali intake. They state that, taken individually, none of these points excludes primary hyperparathyroidism, but taken as a group they constitute strong evidence against that disease, and in one of their patients who died the parathyroids were not located at necropsy. Kyle (1954) has discussed the above points, and throws some doubt on their validity even when considered together. He cites a case which conformed with the criteria of Burnett *et al.* but in which a parathyroid adenoma was subsequently demonstrated. It is evident that the differentiation of the chronic milk-alkali syndrome from primary hyperparathyroidism may be very difficult, an added complication being the fact that peptic ulcer is not infrequently a feature of the latter disease.

Accepting that the chronic milk-alkali syndrome does, in fact, represent an entity, we feel that our own case corresponds sufficiently to include it as a further example of the condition. Particularly strong evidence for its being so is the general improvement in well-being after withdrawal of Rennie's tablets, with the fall of urea, the rise of the haemoglobin, and the presence of osteosclerosis rather than any evidence of bone destruction. The changes in the calcium levels are difficult to interpret, but we suggest the following course of events. The chronic renal failure had depressed the serum calcium into the normal range when the patient was first seen by us. Presumably, if the calcium had been estimated prior to the onset of severe renal damage it would have been found to be elevated. With the initial improvement in renal function the calcium rose and persisted at hypercalcaemic levels for some months. Persistent hypercalcaemia was also described in some of the original chronic cases and is unexplained. Gradually, on account of the low calcium diet and high fluid intake, the calcium fell back into the normal range. The rise in the urea which latterly occurred may also have contributed to this. The occasional presence of pus cells in the urine suggests a chronic pyelonephritis which may have existed prior to the onset of the present condition or merely represents a complication of it. The ocular calcification also seems to be strong evidence in support of the diagnosis, since of 19 cases of chronic milk-alkali syndrome described in the literature 16 had such calcification in the form of conjunctival crystals or a band keratitis best revealed by slit-lamp examination. Pruritus was present in 10 cases, though it is probably a reflection of renal failure and therefore non-specific. It was a leading symptom in our patient. Alkalosis occurred in 10 cases, in four the alkali reserve was normal, and in the remaining five (including four fatal cases) acidosis was present, as in our case. Acidosis probably represents a later stage in the syndrome, and is indicative of severe renal damage.

The widespread osteosclerosis, which is greatly against a diagnosis of primary hyperparathyroidism, is of interest. Burnett *et al.* (1949) noted periosteal new bone formation in one of their cases and demonstrated dense cortical bone in another by bone biopsy. Reifenstein (1958), in a general discussion on bone metabolism, states that increased matrix calcification does not occur. Unfortunately, we did not measure the proportion of mineral phase of the bone in our patient. The radiological findings coupled with those of the bone biopsy indicate that increased trabeculation and new bone formation had occurred, and it is reasonable to link this up in some way with the gross increase in calcium intake. Another explanation is that the osteosclerosis may be secondary to the renal failure (Crawford *et al.*, 1954).

All but one of the cases of the chronic milk-alkali syndrome so far reported have occurred in the U.S.A., this perhaps being related to the generous milk-drinking habits and pronounced self-medication in that country. We believe the present case to be the first to have been described in Britain and to be the second time that this syndrome has occurred in a woman.

The exact aetiology of these cases is obscure. Becker *et al.* (1952) noted at necropsy on 99 patients, each with a chronic duodenal ulcer, the presence of renal parenchymal calcification in 36% of them, compared with an incidence of 13% in a non-ulcer control group. In 68% of these cases with renal calcification there was a history of a high intake of alkali, well above the rate in the ulcer cases without such changes. They postulated the occurrence of transient, asymptomatic, hypercalcaemic incidents in these patients taking a high calcium diet. Burnett *et al.* suggest that there is an interference with the renal handling of calcium in such cases, and Kyle offers the following sequence of events: an initial alkalosis causing renal impairment, with a resulting decrease in the renal excretion of calcium, and this, in conjunction with the increased intake, producing the hypercalcaemia. In some of the reported cases the presence of antecedent renal damage has been noted. Carpenter and Pautler (1954) suggest that the chronic milk-alkali syndrome is probably primary hyperparathyroidism with atypical changes due to excess alkali therapy, but, as Kyle points out, it is doubtful if their own case conformed to the syndrome, as no history of excess milk and alkali intake was present.

The prognosis is variable and probably depends in general on the degree of renal damage present by the time the condition is first recognized. Improvement has varied greatly in the reported cases and its extent seemed unpredictable. In some, disappearance of calcinosis was dramatic, particularly from subcutaneous deposits and in those in the region of joints, while in others little change was evident.

Summary

A case of the chronic milk-alkali syndrome following prolonged excess intake of alkali but not of milk is described. A favourable response was obtained after withdrawal of alkalis and the prescription of a low calcium, high fluid intake. An interesting feature was the generalized osteosclerosis.

We are grateful to Dr. J. McIntosh for permission to publish this case. We are indebted to Dr. B. E. C. Nordin, who often advised us on the management and carried out some of the special investigations. We thank Dr. J. W. Chambers for much useful advice and co-operation, and Dr. R. J. McWilliam for the ophthalmological examination.

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LATE RESULTS AND PROTEIN STUDIES AFTER PARTIAL GASTRECTOMY

BY

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In a recent investigation into the incidence of coronary ischaemia after partial gastrectomy (Walker *et al.*, 1958), a study was made of 40 male gastrectomy patients in whom a Polya type of operation had been performed approximately 10 years before. This provided the opportunity for a simultaneous study of the long-term incidence of post-gastrectomy symptoms, and as each patient had previously been interviewed by one of us in 1952–3 (Anderson *et al.*, 1955) it was possible to make an assessment of their clinical progress.

The incidence of nausea, bilious vomiting, and dumping is initially high after operation (Muir, 1949), but in most cases improvement is rapid and symptoms lessen or disappear in the first few months. Clinical experience suggests that there is a tendency towards improvement after the first post-operative year, but information about the late results is scanty.

Loss of weight is a common sequel of the operation (Anderson *et al.*, 1955), and the labelled-fat studies of Everson (1954) suggest that fat absorption may be impaired in some cases. Evidence of increased nitrogen

loss in the faeces (Wollaeger *et al.*, 1946) suggests that protein absorption may also be impaired, and we undertook estimations of plasma protein levels in these 40 patients to determine whether any alterations had occurred.

Methods

Forty men over 45 years of age were interviewed, each having undergone a Polya type of partial gastrectomy for duodenal ulcer about 10 years previously (mean 9 years 10 months; range 7 to 13 years). The mean age at operation was 44 years. The incidence of post-gastrectomy symptoms and loss of work for any reason was ascertained, loss of weight was estimated, and haemoglobin was measured by the Eel colorimeter. This information was also available from the 1952 survey (Anderson *et al.*, 1955), and the findings were compared.

Total plasma protein was estimated by the Biuret method. Albumin/globulin fractionation was performed with sodium sulphate, and the absolute values given in this paper are obtained from this chemical separation. Electrophoretic separation of the protein fractions was carried out on each specimen using the standard Eel method, and the strips were stained with azocarmine B before planimetry.

The same estimations were carried out in two other groups of similar age—namely, a group of 40 male patients suffering from chronic duodenal ulcer, and a group without digestive symptoms who were admitted to hospital for routine surgical operations.

Results

Post-gastrectomy symptoms have been classified as follows: (1) Nil (a feeling of fullness after meals was disregarded); (2) mild symptoms of bilious vomiting and/or dumping; (3) severe symptoms of bilious vomiting and/or dumping; and (4) hypoglycaemia. Twenty-seven patients were symptom-free at both interviews (1952 and 1957); seven showed no alteration in symptoms; five stated their symptoms had disappeared during the five-year period; and one developed mild bilious vomiting in his seventh post-operative year. The details are recorded in Table I.

TABLE I.—*Alteration in Symptoms*

Change in Symptoms	No. of Patients	Symptoms 1952	Symptoms 1957
No change (34)	27	Nil	Nil
	3	B.V. and D.	B.V. and D.
	1	B.V.	B.V.
	1	B.V. and D. ++	B.V. and D. ++
	1	B.V. ++	B.V. ++
	1	D. ++	D. ++
Improved (5)	1	B.V.	Nil
	3	D.	"
	1	Hypoglycaemia	"
Worse	1	Nil	B.V.

B.V.=Bilious vomiting. D.=Dumping. ++=Severe symptoms.

Of eight patients who suffered from mild bilious vomiting or dumping in 1952 (Table I), four experienced relief of symptoms by 1957, and in one of these relief of dumping was achieved by converting his Polya gastrectomy to a Billroth I type in 1956. The other four showed no change. One patient who suffered from hypoglycaemia ultimately became free of symptoms. Three patients whose symptoms were severe did not improve at all (Table I).

Comparison of the recorded weights showed that the group mean was 131 lb. (59.4 kg.) in 1952 and 132 lb. (59.9 kg.) in 1957, there being only nine patients in whom a weight difference of more than 4 lb. (1.8 kg.) was found. One who developed pulmonary tuberculosis lost 16 lb. (7.3 kg.), and the patient who had a Billroth conversion gained 11 lb. (5 kg.). Those in whom post-gastrectomy symptoms disappeared did not gain weight.

The mean haemoglobin levels were 84.8% in 1952 and 88.2% in 1957, but there was a wide range of individual differences, as 19 patients varied by 10% or more. Five patients who were anaemic (70% or less) in 1952 had responded to treatment with oral iron, but a sixth had relapsed. Two others developed an iron-deficiency anaemia (75→63% and 85→59%). The patients with symptomatic improvement showed no material improvement in haemoglobin.

Comparison of work records showed that these 40 men lost a total of 297 weeks in 1952 and 234 weeks in 1957, the principal cause of the difference being the improved employment record of three men. The high average loss per man is due to the poor record of a few, as 60% lost no work in either period. There was a close correlation between work lost and the severity of post-gastrectomy symptoms.

In Table II the mean values for total protein, albumin, and globulin obtained by the Biuret method are recorded for the three groups of patients. The mean values of total protein show significant differences ($F=4.2$; $P<0.05$): the difference between the gastrectomy control groups is highly significant ($t=2.9$; $P<0.01$). Albumin mean values are not significantly different ($F=1.6$), but a real difference may possibly exist between the gastrectomy and control groups ($t=1.76$; $0.05<P<0.1$). Globulin mean values suggest significant differences between the groups ($F=2.6$; $0.05<P<0.1$) and a t-test shows that a significant difference exists between the gastrectomy and control groups ($t=2.26$; $P<0.05$).

TABLE II.—*Mean Values of Plasma Proteins (g./100 ml.) (Biuret Method)*

Group	No. of Patients	Total Protein	Albumin	Globulin
Gastrectomy ..	40	7·00	4·87	2·13
Ulcer	40	7·21	4·97	2·24
Control	40	7·37	5·06	2·30

The expected weight of each gastrectomy patient was calculated from height and age tables (Levine, 1923), and grouped according to the difference between this and actual weight. The majority were below expected weight, but no correlation between the difference (expected weight minus actual weight) and plasma protein levels was found (Table III). There was also no correlation between protein levels and actual weight.

When the globulin fraction had been analysed by planimetry the results were expressed as a fraction of total globulin, as assayed by the Biuret method (Table

TABLE III.—*Relation of Protein to Weight in 40 Gastrectomy Patients*

Amount Below Expected Weight		No. of Cases	Mean Plasma Proteins (g./100 ml.)		
lb.	kg.		Total	Albumin	Globulin
<7	<3·2	5	7·05	4·82	2·23
<21	<9·5	11	7·13	4·92	2·21
<35	<15·9	17	6·93	4·94	1·99
<36	<16·3	7	6·90	4·64	2·26

IV). The differences were found to be slight, but the following were statistically significant: α_2-globulin in the gastrectomy group is lower than in the other groups ($P<0.01$), and α_2-globulin is lower in both gastrectomy and ulcer groups than in the control group ($P<0.01$).

TABLE IV.—*Electrophoresis of Plasma Proteins—Mean Values (g./100 ml.)*

Group	Globulins			
	α_1	α_2	β	γ
Gastrectomy ..	0·23	0·39	0·56	0·96
Ulcer	0·25	0·50	0·60	0·90
Control	0·29	0·54	0·63	0·84

Discussion

Improvement in post-gastrectomy symptoms is common in the early months (Muir, 1949), and these results show that late improvement is also possible in mild cases, though less likely when symptoms are severe. Late deterioration as described by Wells and MacPhee (1954) was found in one patient.

The majority, however, show little change over the five-year period, and the weight of each patient has been remarkably stable, though weight normally tends to increase with advancing years. Johnston *et al.* (1958) showed that gastrectomy patients gained weight with intensive dietary supervision, but the increase was small and not necessarily maintained when the diet returned to normal. In our patients whose symptoms improved there was no corresponding rise in weight.

While none of our cases showed levels comparable with the low serum albumin described by Forshaw (1958), the significant difference between the total protein and globulin mean values of the three groups is interesting. This may indicate a poorer absorption of protein or merely reflect a lower intake by gastrectomy patients; the intermediate position of the ulcer cases may bear a relation to altered diet. The significant, or probably significant, difference in the group comparison tends to confirm the view. An attempt to relate this to weight was unsuccessful. The significance of the alteration in α_2-globulin fraction is not apparent.

In another investigation (Walker *et al.*, 1958) it was found that the serum lipoproteins of gastrectomy patients did not differ to any significant extent from those of ulcer and other patients.

Summary

Studies of 40 patients 10 years after Polya gastrectomy showed relatively little change in post-gastrectomy symptoms, weight, or work records between 1952 and 1957, though late symptomatic improvement occurred in four cases and late deterioration occurred in one. Improvement in symptoms was not associated with a gain in weight or haemoglobin.

Measurements of total plasma protein, albumin, and globulin, and electrophoresis of plasma proteins indicate that total protein and α_2-globulin may be lower after Polya gastrectomy, but no gross deviations from normal were found.

Our thanks are due to Professor C. F. W. Illingworth for the facilities granted, and to Dr. R. A. Robb for advice and help with the statistics involved.

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NON-ADDISONIAN MEGALOBLASTIC ANAEMIA, COMPLICATED BY SUBACUTE COMBINED DEGENERATION OF THE CORD

BY

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Subacute combined degeneration of the cord (S.C.D.) is classically associated with Addisonian pernicious anaemia and is attributed to malabsorption of vitamin B_{12}, due to lack of intrinsic factor consequent on gastric atrophy. S.C.D. may, however, occur in any type of non-Addisonian megaloblastic anaemia due to vitamin-B_{12} deficiency. One such type is associated with structural intestinal changes such as fistulae or anastomoses, with diversion of vitamin B_{12} by bacteria in stagnant areas of bowel, and another with malabsorption of vitamin B_{12} due to short-circuit operations or small-bowel infiltration by tuberculosis or tumour. Richmond and Davidson (1958) found only five cases of each type in the literature, and described one further case of each type of their own.

The case presented here had certain features common to both types, since there was a megaloblastic anaemia, normal gastric acidity, S.C.D., operative and radiological evidence of intestinal anastomosis and fistula formation, biochemical evidence of a malabsorption syndrome with steatorrhoea, and impaired absorption of ^{58}Co-labelled vitamin B_{12}.

Of additional interest was the time relationship of the neurological signs to isoniazid therapy.

Case Report

In 1940 the patient had a gastro-jejunostomy performed at the Glasgow Royal Infirmary for a chronic duodenal ulcer. He was readmitted in 1943 with symptoms due to chronic indurated prepyloric and stomal ulcers. At operation the site of the gastro-jejunal anastomosis was firmly adherent to the transverse colon. The previous anastomosis was left untouched and a new gastro-jejunostomy was performed. Three years later he was again admitted because of further ulcer symptoms, and vagotomy was done, with considerable relief of symptoms.

In 1950 he was first admitted to Stobhill General Hospital with a six-months history of diarrhoea, and a barium-meal examination showed a gastro-colic fistula. Ileo-sigmoid-ostomy was performed and the patient discharged to out-patient supervision.

He remained well until 1951, when he was readmitted to Stobhill Hospital with a recurrence of diarrhoea. Haemoglobin was 14 g./100 ml., and a blood film normal.

The fat content of the stools was greatly increased (53.4% of the dried specimen): 54.7% was split and 45.3% was unsplit. This was attributed partly to intestinal hypermotility and partly to malabsorption consequent on his gastro-jejunostomy. A gastric test meal showed a high acid curve despite his previous vagotomy, and a barium-meal examination revealed a well-functioning gastro-jejunostomy. He was discharged, having two well-formed stools per 24 hours.

For the next five years he was seen periodically as an outpatient, during which time he remained at work and free from ulcer symptoms. He continued to have recurrent periods of diarrhoea, during which he passed up to six poorly formed stools per 24 hours; from these no organisms were isolated. During this period steatorrhoea continued.

On June 15, 1955, he was readmitted to Stobhill Hospital because he was passing five or six frothy, greasy stools per 24 hours, the first time these two characteristics had been noted. Stool frequency dropped to two per 24 hours without specific therapy, and he was discharged, only to be again admitted on July 28 with a complaint of night sweats and a clinical finding of dullness at the right base. On admission he was afebrile, the E.S.R. was 3 mm./1 hour, and a chest *x*-ray film showed only pleural thickening at the right base; he was discharged.

For the next 18 months he had no ulcer symptoms, continued to pass two soft stools per 24 hours, and remained at work.

On January 15, 1957, he was readmitted to Stobhill Hospital with a recurrence of night sweats and also left-sided pleuritic chest pain. He was febrile, his E.S.R. was 47 mm./1 hour, and a chest *x*-ray film showed right basal pleural thickening with a small left basal pleural effusion. Blood examination was normal. An axillary lymph node biopsy showed active caseating tuberculosis. Faecal fat excretion remained high, averaging over 12 g. of stearic acid per 24 hours on five successive days (normal >6 g. per 24 hours). His tuberculosis was treated with 1 g. of streptomycin and 300 mg. of isoniazid daily, and he was discharged to a chest clinic where antituberculous therapy was continued until April, 1958.

In May, 1958, he was admitted to our care at Stobhill Hospital because of paraesthesiae of the upper and lower limbs, associated with slight difficulty in walking since January, 1958. The provisional diagnosis was that of peripheral neuritis due to isoniazid toxicity.

He was found to have the signs of peripheral neuritis with muscle-wasting, impaired muscle power, and grossly diminished tendon jerks in all limbs, diminished sensation to pin-prick, and hyperalgesia to deep pressure in the lower limbs, and normal touch sensation. There were no signs of posterior or lateral column involvement, since vibration and postural sense was normal, there was no muscle spasticity, and both plantar responses were flexor. Haemoglobin was 14.6 g./100 ml. with a normal blood film. Barium-meal examination showed a well-functioning gastro-jejunostomy with a gastro-colic fistula, and the mean daily excretion of stearic acid over a period of six days was 20 g.

He had also a pellagra-like dermatitis involving the hands, face, and lower limbs, which disappeared rapidly on treatment with folic acid, 40 mg. by mouth daily, and vitamin-B complex parenterally. There was no change in the neurological picture, and he was discharged to continue folic acid and oral vitamin-B therapy.

He was given six weekly injections of liver extract before his readmission to us on December 19 because of severe diarrhoea. Estimation of stearic acid showed continuing severe steatorrhoea, and the haemoglobin was now 8.6 g./100 ml. Sternal puncture revealed a megaloblastic marrow with normal leucopoiesis and platelet formation. A gastric test meal gave a high acid curve, and a Schilling test showed grossly subnormal urinary excretion of ^{58}Co-labelled vitamin B_{12}, with no increase in excretion when the test was repeated with intrinsic factor. These findings excluded Addisonian pernicious anaemia.

The neurological signs of severe peripheral polyneuropathy were still present, but in addition there was gross ataxia, with Rombergism and impairment of postural, proprioceptive, and vibration senses in the lower limbs, indicating posterior-column involvement. There was also slight muscle spasticity of the lower limbs, suggesting lateral-column involvement, though the plantar responses were flexor.

It was thought that the diagnosis was non-Addisonian megaloblastic anaemia, with neurological manifestations of vitamin-B_{12} deficiency, secondary to malabsorption of vitamin B_{12} in a structurally altered intestine. Folic acid and oral vitamin B were continued, and in addition he was given vitamin B_{12} 1,000 μg. thrice weekly by intramuscular injection. His haemoglobin rose rapidly to 12.4 g./100 ml.; four weeks later his walking had greatly improved and he was no longer grossly ataxic.

Discussion

The earliest sign of neurological involvement in this patient was a polyneuritis which began in January, 1958. The blood picture in May, 1958, was normal, at which time the polyneuritis was well established. After the introduction of folic acid in May, 1958, the onset of the peripheral blood changes of vitamin-B_{12} deficiency was probably delayed, owing to the temporary maintenance of normoblastic erythropoiesis by this treatment. This would suggest that before folic acid therapy is instituted in malabsorption states with steatorrhoea, the possibility of deficiency of vitamin B_{12} should be investigated. This would clarify early neurological signs in such patients, and recognition of the early stages of S.C.D. in non-Addisonian megaloblastic anaemia would be more likely. The introduction of vitamin-B_{12} therapy would then prevent progressive neurological damage.

The progression of S.C.D. and the presence of a megaloblastic marrow following treatment with liver extract are of interest. These findings support the advice of Adams and Timbury (1959) that, because of the poor vitamin-B_{12} content of most liver extracts, cyanocobalamin should always be used.

It is noteworthy that the onset of polyneuritis and pellagra coincided with a course of isoniazid, and it was then thought that both might be related either to a malabsorption syndrome with nicotinic acid and riboflavine deficiency or to isoniazid therapy. Polyneuritis had only rarely been reported as a complication of tuberculosis prior to isoniazid treatment (Harris, 1926; Ford, 1944). Since then several authors have reported polyneuritis in patients with tuberculosis treated with isoniazid (Katz *et al.*, 1944; Dixon *et al.*, 1956). It is believed that polyneuritis is more frequent with high and prolonged dosage schemes (Biehl and Nimitz, 1954), though these authors found that 8% of patients receiving 6–10 mg. of isoniazid per kg. body weight daily developed polyneuritis. Dixon *et al.* (1956) were of the opinion that some patients might develop neuropathy on moderate dosage of isoniazid, and noted that the condition improved spontaneously when the drug was discontinued. It is believed that our patient developed polyneuritis due to vitamin B_{12} deficiency, occurring in an established malabsorption syndrome, and not because of isoniazid therapy or nicotinic acid and riboflavine deficiency. This is supported by the facts that the patient's daily dose of isoniazid never exceeded 6 mg. per kg. body weight,

and that even when the drug was discontinued in April, 1958, the polyneuritis progressed relentlessly until the full clinical picture of subacute combined degeneration of the cord was established by December, 1958. Moreover, this progression, despite treatment with a vitamin-B complex parenterally, suggested that malabsorption of these substances was not the primary cause of his neuropathy.

The skin lesions were believed to be those of pellagra, which is found in chronic deficiency of nicotinic acid and riboflavine (Sydenstricker, 1941). It is probable that the pellagra was caused by grossly impaired absorption of nicotinic acid, and this view is supported by the rapid response of the skin lesions to a parenteral vitamin-B complex. It is possible that isoniazid therapy, by interfering further with carbohydrate metabolism, contributed to the production of pellagra, since it is known that pellagra becomes worse during isoniazid therapy.

It is worth repeating that the neurological signs were unaffected by isoniazid withdrawal, by long-continued dosage of vitamin-B complex and folic acid, or by liver extract given parenterally for six weeks. This suggests that the primary cause was, in fact, a developing vitamin-B_{12} deficiency, which liver extract was unable to prevent, presumably because of its low vitamin-B_{12} content.

Summary

A case of non-Addisonian megaloblastic anaemia with subacute combined degeneration of the cord, associated with severe malabsorption in a structurally altered intestine, is presented. There was a history of tuberculosis treated with isoniazid.

It is suggested that before folic acid is given in the treatment of such cases deficiency of vitamin B_{12} should be excluded, especially in the presence of early neurological involvement.

The possible relationship of vitamin-B_{12} deficiency and isoniazid treatment to the neurological changes is briefly outlined.

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The 1959 edition of the Association of British Chemical Manufacturers' directory, *British Chemicals and their Manufacturers*, is now available. This new edition contains over 12,000 products named systematically and in accordance with British Standard 2474:1954—*Recommended Names for Chemicals Used in Industry*. Copies are available, free of charge, to all persons or firms genuinely interested in the manufacture or purchase of chemicals, from the association, Cecil Chambers, 86, Strand, London, W.C.2.

EXPERIMENTAL STUDIES ON BYSSINOSIS

BY

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Byssinosis is a disease occurring among cotton-mill workers (Schilling, 1956). Its main symptoms are dyspnoea and a feeling of tightness in the chest. These are usually most prominent when the workers return to the cotton-mill after absence from work for a few days, during the week-end, or a holiday. The respiratory symptoms are generally ascribed to the inhalation of the dust produced in the card-rooms of the mills. However, the way in which the dust produces the symptoms of byssinosis is not known. It has been shown that the symptoms are accompanied by a decrease of the maximal breathing capacity and an increase in airway resistance (McKerrow *et al.*, 1958). It has been suggested that histamine or some other active substance in the cotton dust is responsible for the dyspnoea of byssinosis. According to another hypothesis the symptoms are a manifestation of an allergic (antigen-antibody) reaction to the cotton dust (Haworth and Macdonald, 1937).

We have studied the effect of cotton dust on the lung ventilation in two men who had not previously been exposed to the dust in the cotton-mills. Extracts of cotton dust were inhaled in the form of an aerosol, and the changes in the lung ventilation produced by the extracts were studied with the nitrogen clearance method (Bouhuys *et al.*, 1956). This method involves continuous recording of the nitrogen concentration in expired gas during oxygen-breathing. The "lung-clearance index" (L.C.I.) (Becklake, 1952) is the amount of ventilation required to wash out the nitrogen from 1 litre of the lung volume down to 2% nitrogen in end-tidal gas. The clearance of nitrogen from the lungs is delayed, and the L.C.I. increased, in patients with asthma and in normal subjects after inhalation of histamine (Bouhuys *et al.*, 1960).

Experimental

The extracts were prepared from a sample of mixed cotton dust collected in a ventilator in a card-room. 3 g. of the dust was ground with sand in a mortar, 50 ml. of saline was added, and the sample was allowed to stand overnight at 4° C. The sample was filtered the next day and the filtrate used for the experiments. The activity of the extracts seemed to deteriorate with time, and for this reason fresh extracts were always used. The aerosol of the filtrate was produced in a nebulizer (Rooth, 1949) in the same way as histamine aerosols had been produced in a previous investigation (Bouhuys

et al., 1960). The subjects inhaled the extract from the nebulizer for 10 minutes. Immediately after this they started to breathe oxygen, the first inspiration being taken from the level of a normal expiration, and the elimination of nitrogen from the lungs was recorded. This wash-out procedure was repeated at intervals of 10 to 15 minutes during two to three hours, until the clearance of lung nitrogen had become normal again. Similar experiments were performed in the same subjects, using extracts of mixed house dust.

The subjects were both male laboratory workers. Subject B was 48 years of age and healthy; subject C was 33 and healthy at the time of investigation, but gave a history of bronchial asthma, which, however, had not caused more than occasional slight wheezing and dyspnoea for several years.

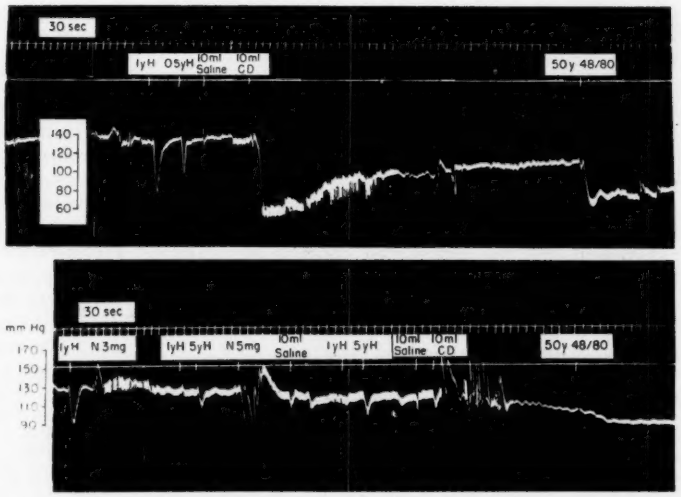
Results and Discussion

The results are summarized in the Table. Inhalation of cotton-dust extract (C.D.) increased the L.C.I. in these two subjects who had not been exposed to the dust in the cotton-mills previously. Inhalation of the house-dust extracts did not increase the L.C.I. In a previous investigation it was shown that inhalation of histamine aerosol increased the L.C.I. (Bouhuys *et al.*, 1960). The weakest histamine solution in the nebulizer that caused a measurable increase of the L.C.I. in subject C contained 5 mg. of histamine base per ml. The corresponding concentration for subject B was 0.05 mg. per ml. Thus B proved to be much more sensitive to inhaled histamine than C. In the present experiments B was found to be more sensitive also to the active agent in the C.D. However, the concentration of histamine in the C.D. was less than 0.001 mg. per ml. when determined with Code's (1937) method. Thus the increase of the L.C.I. caused by the C.D. could not be due to the histamine possibly contained in the C.D.

After inhalation of histamine the highest L.C.I. was usually recorded immediately after the inhalation, and the L.C.I. returned to normal within 15 to 45 minutes (Bouhuys *et al.*, 1960). The effect of the C.D. on the L.C.I. reached its maximum about 20 minutes after the end of the C.D. inhalation, and it lasted for at least one hour. The dyspnoea caused by C.D. was accompanied by a feeling of general malaise.

The increase of the L.C.I. caused by histamine can be repeated on several consecutive days, but the effect of C.D. that had been obtained on first exposure to cotton dust did not occur after a second exposure on the following day. It could, however, be reproduced 5 and 60 days later. These findings are reminiscent of the symptom pattern in byssinosis.

These results of the inhalation of extracts of cotton dust, as well as some of the symptoms of byssinosis, might be explained if the cotton dust contained a substance capable of releasing histamine. We have performed some experiments with animal preparations which support the view that the C.D. used contains a histamine liberator.



Blood-pressure records from two parallel experiments with cats weighing 2.5 kg. and anaesthetized with sodium pentobarbitone. The blood-pressure was recorded with a mercury manometer connected to a carotid artery. 1 γ H indicates intravenous injection of 1 γ histamine base, etc. 10 ml. saline and 10 ml. C.D. indicate intravenous injections of 10 ml. saline and cotton-dust extract respectively. N 3 mg. = intravenous injection of 3 mg. mepyramine maleate (neoantergan). 50 γ 48/80 = intravenous injection of 50 γ of compound 48/80.

When injected intravenously the C.D. caused a fall in blood-pressure in cats anaesthetized with sodium pentobarbitone (30 mg./kg.) (see Fig., upper curve). The fall in blood-pressure occurred after a latent period of about 30 seconds. A similar latent period was observed after injection of compound 48/80, a well-known histamine liberator (Dews *et al.*, 1953; Paton, 1957). The depressor response after injection of histamine, on the other hand, showed a latent period of about 12 seconds. When the same amount of C.D. was administered a second time to the same cat no fall in blood-pressure was observed. In another cat, pretreated with 3 mg. of mepyramine maleate per kg., the same C.D. did not cause any fall in blood-pressure (see Fig., lower curve).

Two isolated segments of guinea-pig ileum were suspended in separate baths, of about 5-ml. volume, containing oxygenated Tyrode solution (33° C.). Addition of 1 ml. of C.D. to the bath caused a slow contraction of the gut, quite different from the contraction elicited by histamine. The contraction reached its maximum after about seven minutes and persisted for

Lung-clearance Index After Inhalation of Cotton-dust and House-dust Extracts in Man

Subject	Date 1958	Inhaled Extract	Lung Clearance Index		Remarks
			Before Inhalation	Maximum Recorded after Inhalation	
C	10/10	C.D.	8·3	10·2*	Dyspnoea
C	11/10	C.D.	8·4	9·1	No complaints
C	10/12	C.D.	7·2	11·0*	Dyspnoea
B	10/10	C.D.	9·1	21·1*	,,
B	11/10	C.D.	11·4	12·6	No complaints
B	15/10	C.D.	9·7	16·5*	Dyspnoea
C	14/10	H.D.	8·4	9·2	No complaints
B	14/10	H.D.	11·4	11·2	,, ,,

C.D. = 10 minutes' inhalation of cotton-dust extract. H.D. = 10 minutes inhalation of house-dust extract.

* Values outside the subject's normal range of L.C.I. (mean ± 2 S.D.), based on 21 control experiments in subject C (mean L.C.I. = 8·2; S.D. = 0·7; S.E. = 0·15) and on 18 controls in B (mean L.C.I. = 10·2; S.D. = 1·6; S.E. = 0·4).

a long time, even though the gut was washed repeatedly with fresh Tyrode solution. The contraction caused by 1 ml. of C.D. could be antagonized completely by mepyramine maleate (0.02 γ/ml. in the bath).

We have thus obtained some evidence that our C.D. contained a histamine liberator, and we should like to advance the hypothesis that some of the symptoms of byssinosis are caused by a histamine liberator in the cotton dust inhaled by card-room workers. Our evidence indicates that the histamine release can take place without a preceding antigen-antibody reaction.

Summary

Inhalation of an extract of cotton dust caused a delay in the clearance of nitrogen from the lungs during oxygen-breathing.

This effect, which presumably is due to bronchial obstruction, was obtained in two men who had not previously been exposed to the dust in cotton-mills.

The effect was not caused by histamine present in the extract.

The results of our experiments, as well as some of the symptoms of byssinosis, may be explained by the assumption that the cotton dust contains a histamine liberator.

Some evidence was obtained, from animal preparations, that the cotton-dust extract used here contained a substance capable of releasing histamine.

We thank Dr. L. Muller, physician-in-chief of the Industrial Medical Service at Enschedé, The Netherlands, for supplying us with the samples of cotton dust.

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In America six deaths from rabies occurred in 1958 and five in 1959 up to November 27. Of the 11 cases, five are attributed to dog bites, three to bites from bats, one to a bite from a fox, one to a bite from a skunk, and one unknown. While in the U.S.A. the animal mainly responsible for transmission is the dog, more and more evidence has been brought forward to show the importance of the bat in maintaining the infection in wild-life and causing infection in man. Since the first U.S. report of bat rabies was made in Florida in 1953, 359 cases of bat rabies have been reported in the U.S.A.; rabies in wild animals is found most frequently in the skunk, 1,005 cases being recorded in 1958. In Germany the bat appears not to be important in maintaining the infection in nature. The main reservoir is the fox: in 1958 1,017 cases of rabies in foxes were recorded in the Federal Republic. In Iran, rabid wolves are the greatest danger. The Iran Pasteur Institute reports, from 1949 to 1958, 443 persons bitten by wolves, with 39 deaths. Elsewhere, the dog plays the most important role. The complexities of the situation are, however, considerable, as exemplified by the Institut Pasteur of Algeria, which reports the following rabid animals in 1958: 915 dogs, 91 cats, 27 rats, 13 head of cattle, 10 donkeys, 9 jackals, 4 monkeys, 2 mice, 1 fox, and 1 rabbit. (W.H.O./55.)

EFFECT OF MENSTRUATION ON SCHOOLGIRLS' WEEKLY WORK

BY

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Menstruation has from the earliest times been regarded as an evil omen. Primitive and civilized people have made it the subject of endless taboos. Slowly and painstakingly evidence is accumulating which reveals the effect of menstruation on the different aspects of a woman's life (Morton *et al.*, 1953; Cooke, 1945; Bickers and Woods, 1951; MacKinnon *et al.*, 1959; Dalton, 1959). The more this knowledge is appreciated the more sympathetically can we regard the vagaries of womanhood, with the inequalities thrust upon her by hormonal variations of the menstrual cycle. This investigation was prompted by observing the mental dullness of many women when interviewed during the premenstruum.

In this study an analysis of data supplied by a girls' school is collated to show the effect of menstruation on general schoolwork, and, secondly, personal observations at another school suggesting its possible correlation with the behaviour of the schoolgirl.

Method

The data were collected from a public boarding-school for girls in south-east England during the autumn term. It is the custom at this school for each subject of the girls' work to be marked from 10 to 0 and these marks to be averaged each week, giving a weekly mark. The form mistresses of 15 forms supplied details of the weekly marks of 352 girls, aged between 11 and 17 years inclusive, and the matron supplied the dates of the girls' menstruations, which each girl entered in the usual book when collecting sanitary towels. The data were obtained without the knowledge of the teachers or girls. Bearing in mind that the weekly mark represents the average of 7 to 12 different subjects, marked by as many different teachers and covering 15 forms, it will be appreciated that the effect of an exceptionally difficult piece of work in one form in one subject or the inconsistent marking by a teacher due to her menstrual variation will be lost in the average of the weekly mark. In the analysis the weekly mark of each girl is compared with her mark in the week immediately preceding it to note if a rise or fall in grade has occurred; this necessitates the exclusion of the first week of term, the week following half-term holiday, and the week following any absences, as there is no weekly mark during the week immediately preceding it with which to compare.

Difficulties of definition arise because the school week has only five working days. The most marked symptoms of the premenstruum occur within the five days immediately preceding menstruation (Greene and Dalton, 1953), so for the purposes of this investigation the "premenstruum" was defined as the five days immediately preceding menstruation, and the "premenstrual" week as the week which contained at least three premenstrual days during the five-day school week. Similarly, the "menstrual" week was defined as

one in which menstruation was present for at least three of the five schooldays, and the "post-menstrual" week as one in which at least three of the five schooldays occurred during the five days immediately following menstruation. "Intermenstrual" weeks were those which did not fall into the previous three categories. Thus if one girl's menstruation lasted from a Friday until the following Monday, the week in which menstruation started would be the "premenstrual" week and the following week would be the "post-menstrual" week. This accounts for the apparent differences of figures; for the total of 1,560 weekly marks available for analysis from the 217 menstruating girls included 324 premenstrual weeks, 342 menstrual weeks, 315 post-menstrual weeks, and 579 inter-menstrual weeks.

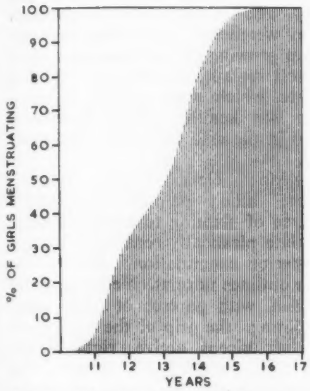

FIG. 1.—Menstruation at various ages (352 girls).

During the 12-week term 135 girls had no menstruation, 28 girls one, 73 girls two, and 116 girls had three or more regular menstruations. Fig. 1 shows the percentage of girls menstruating in the various age-groups, which is a normal curve for English schoolgirls. As 45% of the girls had only one or two menstruations during the 12-week term it follows that some of the "intermenstrual" weeks correspond to a missed menstrual period, and therefore these weeks are better regarded as an average of all weeks.

Results

Falls in the weekly marks compared with the previous week were noted in 27% of the girls during the premenstrual week, in 25% during the menstrual week, and in only 10% during the post-menstrual week. In direct contrast to these figures a rise in weekly marks was shown in 17% of girls during the premenstrual week, in 21% during the menstrual week, and in 30% during the post-menstrual week (Fig. 2). This fall in the standard of school work in 27% during the premenstruum and an improvement in the work in 30% following menstruation reveals the significance of menstruation as a factor affecting the day-to-day performance of schoolgirls (Fig. 3). Further analysis of these weekly marks revealed that this pattern of premenstrual fall and post-menstrual rise was equally present in all age groups, and also occurred equally among girls with only one menstruation per term and those girls menstruating regularly, equally among the bright girls (more than six months below the average age for the form) and the duller girls (more than six months above average age), and was equally distributed among the consistent workers, who had a variation of only two marks during the term, and the inconsistent workers, whose weekly mark fluctuated over four or five grades.

In considering the effect of a few off-colour days during the premenstruum on the school work it is well to appreciate that some of the marked work used in determining the weekly mark covers new work learned during class and tested in the same week—for example, mathematical principles, grammatical rules in English, French, or Latin—while in other subjects homework consists in learning work to be tested the following week. Thus the marking during the menstrual week reflects the failure to learn during the premenstrual week and also the improvement in performance consequent upon the relief of water retention accompanying the full menstrual flow.

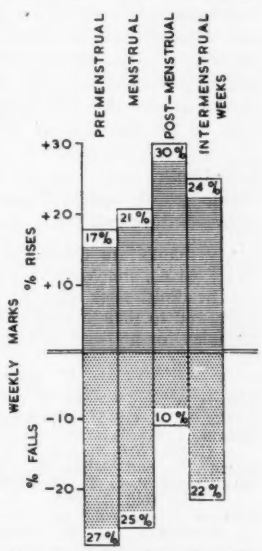

FIG. 2.—Effect of menstruation on 1,560 weekly marks.

Though it was not possible to prove statistically, it would appear that the schoolgirl's behaviour may also be adversely affected by menstruation. The charts in Fig. 4 were seen displayed in the dormitory of a London independent school for girls (mixed day and boarders). Here each morning the 24 boarders in the middle school, aged 10 to 14 years, receive a grade, A to D, from the matron for tidiness of her bed and drawer. An interesting pattern is revealed with falls in tidiness grades occurring at intervals of 21 to 30 days. Though the dates of menstruation were unknown in all the girls except Girl I, it is significant that each of her three falls in tidiness grade coincided with menstruation. Was premenstrual tension responsible for the carelessness of this schoolgirl before breakfast? And does the same apply to the other girls whose charts are also shown?

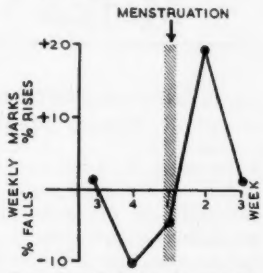

FIG. 3.—Variation in schoolgirls' marks due to menstruation.

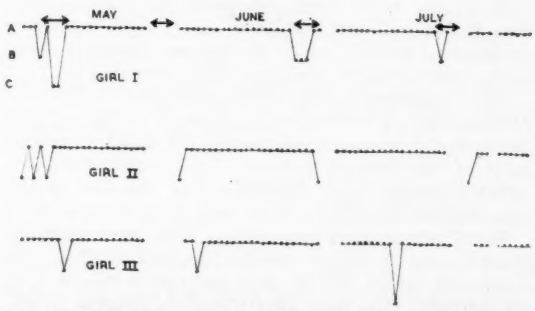

FIG. 4.—Daily tidiness grades with cyclical drops. Girl I: 12 years 6 months; drops in tidiness grades at intervals of 42 and 21 days; menstruation shown by arrows. Girl II: 12 years; drops in tidiness at intervals of 26, 23, and 25 days. Girl III: 13 years 6 months; drops in tidiness grades at intervals of 21 and 27 days.

Summary

The adverse effect of menstruation on the normal school work of 217 menstruating girls, aged 11 to 17 years, is evidenced by the finding that one in every four girls had a fall in weekly mark during the premenstruum followed by a rise after menstruation. It is appreciated that in times of stress the premenstrual symptoms are increased (Dalton, 1955). It would appear, therefore, that on occasions of important examinations the handicap imposed by menstruation will be proportionately increased. About one girl in six in any examination entry will be in her premenstruum and thus at her lowest intellectual ebb. While zealots campaign assiduously for equality of the sexes, Nature refuses to grant equality even in one sex.

My thanks are gratefully expressed to Miss Audrey E. Fryer, M.A., and Miss M. G. Lloyd Thomas, B.Litt., M.A., the headmistresses who so kindly supplied the necessary data, and to their matrons and staff, and also to Dr. E. W. Dunkley for his wise counsel.

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Medical Memoranda

A Case of Phocomelia Associated with Severe Mental Deficiency

Phocomelia is a congenital malformation of the osseous system characterized by the absence or extreme smallness of the arms, forearms, thighs, and legs, producing a pronounced shortening of limbs. The hands and feet, which may be fairly normal in appearance and development, seem inserted more or less direct into the shoulders or pelvis of the patient. As the micromelic appendages resemble the physical outlines of a seal's flippers, the condition is known as phocomelia.*

Sometimes, however, only the arms or the legs are affected and, less uncommonly, a single arm or leg, with all the other limbs otherwise normally formed. The hands and feet, however, may show numerous congenital anomalies, such as disproportionately short, long, supernumerary, and webbed fingers or toes.

This exceedingly rare bone anomaly is related to prenatal factors arising during the early phase of foetal development which prevent the laying down of certain parts of the osseous system. The cranial vault, the vertebral arches, and the pelvic and shoulder girdles may likewise manifest serious structural deficiencies.

Short references to phocomelia have been made by Church and Peterson (1911), Aschoff (1928), and Kaufmann (1929), but the most descriptive record, with photographs, has been contributed by Patten (1946). None of the above-mentioned authors, however, have investigated psychologically the mental condition and intellectual state of their patients.

**Phocos*, Greek for seal. *Melos*, Greek for limb.

CASE REPORT

A case of phocomelia has recently been admitted to this Mental Deficiency Institution. She is a white baby girl aged 3.7 years, having a mental age of 8.2 months and an intelligence quotient of 19, being classified as belonging to a low-grade type of mental defect (idiot).

She is of Caucasian race, and comes from a non-farm rural environment. She is the younger of two siblings, her brother being of normal physique and intelligence, and in good health.

The mother, who is a diabetic with a history of psychosis, was 35 and the father, who has a peptic ulcer, 43 at the patient's birth. Histories of alcoholism in the paternal and psychosis in the maternal grandparents have also been recorded.

The patient was an eight-months child. The mother felt well during the pregnancy, and labour was said to have been uneventful. The baby weighed 5 lb. (2.3 kg.) at birth, and had feet and a left arm growing out of the lower torso and left upper shoulder–chest region, respectively. She had a hare-lip and a cleft-palate, which were recently repaired surgically. Otherwise she was healthy, breathed without difficulty, and moved about in the crib playfully. No other information was available.

Physical Examination.—Skin: clear. Scalp: normal. Hair: fair and fine. Eyes: blue; palpebral fissures are narrow, with a certain degree of slanting towards the outer angles. Nose, lips, and palate plastically repaired. Lungs: clear to anterior and posterior examination. Heart: no murmurs heard and cardiac outlines normal. Neuromuscular system: she is right-handed, with pareses of both lower extremities and left upper limb; the grip of the right hand is normal; reflexes of left biceps active, right triceps sluggish: left biceps and triceps reflexes are absent; the upper and lower abdominal reflexes, both left and right, are active, and the plantar reflexes are normal bilaterally.

Special data.—Weight on admission, 14 lb. 6 oz. (6.5 kg.). (In the three weeks since her admission she gained over 1 lb. 4 oz. (560 g.) in weight.) Length, 22 in. (55.9 cm.). Cranial circumference, 17½ in. (43 cm.). Length of normal right arm and forearm, 9 in. (23 cm.): shortened left arm and forearm, 5 in. (12.7 cm.). The lower limbs measure only 7½ in. (19 cm.), including the feet. Torso/Leg ratio, 19/14½ in. (48/37 cm.). The inner aspect of the skin of the shortened arm is adherent along the axillary line to the skin of the outer chest wall; the left elbow-joint is movable and the left forearm very short. There is syndactylism of both feet, involving the second and third as well as the fourth and fifth toes, which are unusually small. A pilonidal sinus is seen in the ilio-coccygeal region.

Roentgenological Report.—There are most amazing osseous defects in this child. The left humerus, radius, and ulna are underdeveloped and deformed, but the bony outlines of the right upper limb are normal. Both femurs are hypoplastic and of abnormal shape, and both tibiae and fibulae are absent. The facial bones, particularly the sphenoid, ethmoid, maxillary, and mandibular structures, are rather smaller than usual, and there is a cleft in the bony palate. The left shoulder-blade is hypoplastic, of irregular outline, and shows some defect in its centre. The cranial vault exhibits slight digital markings, with some thinning of the inner table.

Orthopaedic Consultation.—Congenital absence, multiple, in extremity bones; left upper and both lower limbs markedly shortened. Cleft palate, harelip repaired. Later in childhood, if indicated at that time, prosthetic considerations may be given.

Ophthalmological Consultation.—Right eye: Pupil 3° regular and active homatropine—media clear; disks clear, good colour; vessels and maculae normal. Left eye, similar to right eye. Examination of media normal. No disease seen.

Psychological Consultation.—Gross motor patterns fall between the eight- and sixteen-week levels. Standing, unable to support any weight, below twelve weeks; supine, pulled to sitting, complete head-lag twelve weeks; prone, head zone III 16-week level. Adaptive patterns are somewhat higher; that is, radial palmar grasp 28 weeks; and transfers adeptly, 28 weeks. No verbalization elicited. Sphincter control absent; cannot sit up or feed herself. Chronological age: three years seven months; mental age, eight and two-tenths of a month; intelligence quotient 19. Classification: idiocy.

CONCLUSIONS

In view of the above findings, it appears that this child manifests the congenital malformation described as phocomelia, which is complicated by a severe degree of intellectual defect (idiocy), cleft-palate, hare-lip, skull anomalies, pedal syndactylism, and pilonidal sinus.

I am indebted to Mr. James Dutremaine, an employee at Letchworth Village, for the photograph of the patient.

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Scorbutic Arthritis Complicating Triamcinolone Therapy

A case is described below in which fleeting muscle and joint pains followed by arthritis and effusion in the knee-joint associated with vitamin-C deficiency occurred in the course of triamcinolone therapy.

CASE REPORT

A man aged 50 was admitted to hospital on February 27, 1958, for investigation of bilateral basal pulmonary fibrosis. He gave a one-year history of progressive breathlessness, but nothing referable to any other system, and no past history of rheumatic trouble. He said that he had always taken a good mixed diet, and was fond of green vegetables and fresh fruit.

On examination he was well nourished, and there were no signs of avitaminosis. Physical examination was negative apart from the presence of marked finger- and toe-clubbing and central cyanosis. In addition crepitations were present at the bases of both lungs. Detailed examination of his other systems revealed nothing abnormal, and all laboratory investigations were within normal limits. Lung biopsy was carried out and the diagnosis of Hamman–Rich syndrome was confirmed on microscopical examination.

On May 9 he was started on triamcinolone, 16 mg. a day, in the hope of preventing extension of the pulmonary fibrosis, and on June 26 the dose was reduced to 8 mg. a day because of the improvement in his general condition. By July 25 marked moon-face had developed, but the blood picture and electrolytes remained normal. In view of this, and because of the absence of any other physical abnormality and of any deterioration radiologically, it was decided to continue with triamcinolone. By September 4 his condition had deteriorated. On examination he was more breathless and he had a marked tachycardia. His weight had fallen from 11 st. to 10 st. 2 lb. (70.3 to 64.4 kg.), but, apart from his moon-face, no fresh abnormality was found on clinical examination. His blood chemistry and electrolytes remained as before. By September 25 he was *in extremis*. His triamcinolone was increased to 16 mg. t.d.s., and on this massive dosage he improved dramatically. The blood chemistry remained normal.

He developed a purpuric rash on the legs and feet on October 2 and fleeting muscle and joint pains on October 26. His dose of triamcinolone was slowly reduced. On October 30 pain was localized to the left knee, which was stiff and swollen. There were clinical signs of effusion into the joint, but *x*-ray examination was negative. The knee was treated with support and rest, but remained swollen and painful. The rash also persisted. At this time the dose of triamcinolone was 4 mg. t.d.s.

On November 13 ascorbic-acid-saturation tests were started, 650 mg. of vitamin C being given each morning and the urinary excretion of vitamin C being measured in the 10 a.m.–12 noon collection. The normal excretion value (greater than 50 mg.) was not reached for seven days, by which time the rash was fading and the joint pain and swelling had disappeared. Triamcinolone had not been discontinued.

COMMENT

Arthritis has been reported by Polley (1956) as a complication of corticosteroid therapy. Indeed, he quotes Slocumb (1953), who described characteristic fleeting muscle and joint pains as a symptom of hyper-cortisonism. Arthritis has also been described as a complication of triamcinolone administration (Wells, 1958), while the development of scurvy has been observed in patients on long-term corticosteroid therapy (Stefanini and Rosenthal, 1950; Holley and McLester, 1951). The case described above would appear to combine all these abnormalities. It is not recorded whether or not there was any evidence of scurvy in the earlier patients suffering from arthritis.

Chamberlain and Addison (1958) described the development of scurvy after bilateral adrenal-ectomy. It is highly probable that the same mechanism operated in the case described above, in that the massive doses of triamcinolone given would totally suppress the patient's own adrenocortical function.

In view of the findings in this case it is probably desirable that patients given long-term corticosteroid therapy, and in particular patients receiving triamcinolone, should be given vitamin-C supplements. The patient described above has been kept symptom-free despite continuing triamcinolone therapy on 50 mg. of ascorbic acid twice daily.

I thank Dr. C. Kelman Robertson for his permission to describe a case under his care, and for his encouragement in the writing of this report.

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Bilateral Pulsating Exophthalmos Due to Metastases from Carcinoma of Prostate

The orbit is a rare situation for blood-borne metastases. Only four cases of secondary deposits in the orbit from carcinoma of the prostate have been found in a search of the literature. There is not a single recorded example of pulsating exophthalmos due to metastases from this or any other primary site.

CASE REPORT

In November, 1957, the patient, a man of 73, noticed one morning that he was seeing double. The two objects were one above the other when he looked up and side by side when he looked to the right. At about the same time he noticed a humming in both ears, which gradually increased until he said that he could hear a noise like marching feet, which appeared to come from the left side of his head. Shortly afterwards he began to get a deep aching pain in his right leg, left arm, and back, and noticed that his hearing was less good than formerly. He felt perfectly fit in himself, was eating and sleeping well, and said that he felt like a man of 40. At this time he had no abnormal urinary symptoms at all, but apparently in 1955, following a partial gastrectomy for a peptic ulcer, he developed retention of urine, requiring suprapubic drainage for a short period. At that time his prostate was felt to be enlarged, but there was no evidence of malignancy. He had no recurrence of this trouble subsequently.

He was admitted to Hackney Hospital under the care of Dr. J. A. Cardno, with whose permission he was transferred to University College Hospital for further investigation. At Hackney it was thought likely that the cause of his symptoms was an arteriovenous communication in the cavernous sinus, but secondary carcinomatous deposits were regarded as another possibility.

On examination on March 1, 1958, there was obvious pulsating exophthalmos on the left side. The eye was pushed outwards and downwards and felt abnormally firm to palpation; there was no chemosis (Fig. 1). The right

FIG. 1 FIG. 2

FIG. 1.—Photograph taken on March 1, 1958. FIG. 2.—Photograph taken on June 5, 1958.

eye was also pulsating, but this was only just perceptible. The fundi were normal apart from a small haemorrhage on the left side. A loud systolic bruit was audible all over his face, maximal over the left orbit. The murmur disappeared on carotid compression on either side, the patient noticing its abolition immediately. No abnormality was found in his arm or leg to account for his complaint of deep aching pain. On rectal examination there was hard, irregular enlargement of the prostate.

Investigations.—Hb, 47%; R.B.C., 2,340,000/c.mm. Sternal marrow: there were few red- and white-cell precursors but many small clumps of malignant cells. E.S.R., 39 mm. in one hour (Wintrobe). Serum acid phosphatase, 42.8 K.A. units. Serum alkaline phosphatase, 31.9 K.A. units. Serum calcium, 9.6 mg./100 ml. Serum phosphorus, 3.5 mg./100 ml. *X*-ray examination of the chest showed collapse of the left lower lobe, with a small pleural effusion, and the ribs and clavicles were riddled with deposits. The pelvis and skull also contained many deposits, both osteoplastic and osteolytic in nature. There was a large osteoplastic lesion in the floor of the left anterior fossa. The left carotid arteriogram was normal. Readings on the Hertel exophthalmometer were: right eye 16.5 mm., left eye 21.5 mm., both the mean of three readings.

On April 3 treatment was started with stilboestrol. 5 mg. t.d.s., which was gradually increased to 10 mg. t.d.s. Within a week the proptosis had obviously receded and the bruit was only just audible and no longer appreciated by the patient. Active osteoblastic activity was indicated by a fall in both the serum calcium and the serum phosphorus, while the alkaline phosphatase rose to 132 K.A. units. The urine calcium was very low at 0.03 g./24 hours. At first his anaemia did not respond to the therapy and he was transfused with 1 pint (500 ml.) of whole blood. After this there was a slow response and his Hb rose to 78% in the course of a few weeks. After his discharge he was seen at intervals in the out-patient department. When last examined on June 5, 1958, his only complaint was of slight ankle oedema. His proptosis had receded further (Fig. 2) and the exophthalmometer readings were right eye 15 mm. and left eye 17 mm. All his pain had disappeared and he felt extremely well. His haemoglobin was 78%, alkaline phosphatase 117 K.A. units, and acid phosphatase 4.3 K.A. units.

COMMENT

The only previous reports of pulsating exophthalmos have been in cases of an arteriovenous shunt in the cavernous sinus or in developmental anomalies in the sphenoid and frontal bones. In the above case the bilateral pulsation and loud bruit seemed to suggest an arteriovenous fistula, but the absence of chemosis, an almost invariable accompaniment of this lesion, was against it. The presence of a recently enlarged unruptured aneurysm in the cavernous sinus was also considered, though this would not have accounted for the loud bruit. Both these possibilities were discounted on the finding of a normal arteriogram. Also against a purely vascular cause was the hardness of the orbit to palpation, which suggested a retro-orbital tumour, and this was supported by the finding on *x*-ray examination of a secondary deposit in the roof of the orbit.

The mechanism of the bilateral nature of the pulsation in this case must remain speculative. If the pulsation had been transmitted from the cerebrospinal fluid, on account of erosion of the orbital roof on each side, a bruit would not have been expected, and the most likely explanation would appear to be that there were two separate highly vascular metastases, one in each orbit. Support for this is given by the exophthalmometer readings, which after two months' therapy showed a reduction of 4.5 mm. in the left eye and 1.5 mm. in the right. The change in the right eye was unlikely to have been due to the loss of fluid, as the patient in fact developed peripheral oedema during the course of treatment.

I thank Dr. E. A. Blake Pritchard, under whose care the patient was admitted to hospital, for permission to publish this case and also for his help in the preparation of this report.

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Reviews

CANCER TREATMENT

Treatment of Cancer and Allied Diseases. Volume I. *Principles of Treatment.* Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. Second edition. (Pp. 646+xxi; illustrated. £8.) London: Pitman Medical Publishing Co., Ltd. 1958.

This is certainly going to be a great work and no mistake. Nine volumes at £8 apiece (at any rate that is what Volume I costs) must make even a librarian look to his budget. But such is the authority behind this production that the publishers are no doubt assured of a market. Multi-volume works on cancer are the fashion, and in Great Britain we already have one, published by Butterworths and edited by Raven, now complete, and a second, arranged a little more logically as a series of monographs and under the general editorship of Smithers, from E. and S. Livingstone. It is therefore perhaps protesting too much to claim that Pack and Ariel is "unique" as the dust-cover does. It is stated to be a second edition of the three-volume work published in 1940, but one finds that Ariel has taken the place of Livingston in the editorship and that John D. Rockefeller, jun., now joins the late Dr. James Ewing in the dedication in place of Dr. Stewart. There is, in fact, little similarity between the two editions, this volume being far more extensive in scope and authorship. The first 274 pages of Volume I of the first edition have been expanded into the whole 600 pages of this book. Some of it is perhaps a little long-winded—the chapter on radiation protection, for instance, upon which matter national authorities are as yet by no means agreed, and which might well be shorter.

The radiotherapy section (250 pages) comprises the bulk of this volume, in contrast to that on the principles of the surgical treatment of cancer, which occupies but 50 pages. It is of course true that the treatment of cancer by ionizing radiations is still a rapidly expanding specialty, and this is particularly so in the case of supervoltage therapy and in the use of radioactive isotopes. Many of the big machines are described in detail, and it is pleasing to read about some novel methods for applying solid radioisotopes as implants or in applicators—a form of treatment which tended to become neglected during the heyday of teleradium therapy.

Elsewhere there are valuable chapters on chemotherapy and hormone therapy, and on the clinical pathology of tumours with reference to microscopic grading, biopsy, and exfoliative cytology, a method at which American pathologists excel. In the last section, which deals with the end-results of cancer treatment, it is less satisfactory to find, in a book of this scope, no account of the clinical staging of tumours, which is quite clearly essential if in fact the end-results of different methods of treatment are to be compared. This omission towards the end of the volume can be contrasted with the exceedingly detailed list (occupying no fewer than six pages) of all the known occupations which might conceivably lead to the production of cancer and which recalls "Beachcomber's" *Directory of Huntingdonshire Cabmen.*

The whole book is beautifully produced and lavishly illustrated; the bibliography is extensive, but, though each chapter has its own list of references, these are grouped together in a section at the end of the volume, which makes reference rather tiresome. The pagination follows the contemporary American custom of using double columns, which I personally detest, believing that there is only one book which should be printed in this fashion.

MICHAEL HARMER.

PARACELSUS

Paracelsus. An Introduction to Philosophical Medicine in the Era of the Renaissance. By Walter Pagel. (Pp. 368+xii; illustrated. Sw. fr. 70.) Basle, New York: S. Karger. 1958.

This book in itself is an intellectual phenomenon. As its title suggests, it may be looked upon in two ways—either as an exposition of the remarkable tangle of observations and speculations published by one of the most controversial of all doctors, Paracelsus, or as a presentation of the basic views of medicine in Renaissance times. Many Lives of Paracelsus have been written. This is like none of them, for the actual biography of Paracelsus occupies only the first 50 pages of the book. The remaining 300 pages are composed of an integration of Paracelsus's symbolic speculations with their background. In spite of Dr. Pagel's valiant attempt, it cannot be said that the views of Paracelsus emerge with clarity, probably because Paracelsus himself forcibly rejected reason and depended upon correspondences and symbolism for his intellectual background. The result, from a rational point of view, is confusing, but among this rich mine of symbolic thought one finds some proto-scientific observations. Thus Paracelsus made some statements which his supporters see as anticipations of modern views, but his antagonists have no difficulty in finding a greater number which seem like sheer nonsense. The pugnacious controversy which he himself began during his own lifetime, therefore, has been carried down through history. The fact that it still lives is a tribute to the vivid forcefulness of his personality.

Paracelsus was concerned to destroy the Aristotelian and Galenic principles of mediaeval medicine; he attacked all medical authorities, with the one exception of Hippocrates. In this we may find ourselves in sympathy with him, but he replaced these ideas with speculations founded on the ideas of the Gnostics and neo-Platonists. The only other writer besides Hippocrates whom he treats with sympathy is Marsilio Ficino of Florence, a man who devoted his life to uniting Christian principles with those of alchemy and magic. Thus Paracelsus's constructive attempts to replace the old ideas meet with little sympathy from our present viewpoint. To us his greatest contribution was the introduction of biochemical analysis into medicine. He separated a coagulum from urine which anticipated the discovery of albumin; he made the suggestion that there was acid at times in the stomach. These, and his concept of "chaos" and the "Archaei," were positive contributions which were developed further by Van Helmont's chemistry a century later.

In this book Paracelsus and his background are presented to us with a rare depth of scholarship and understanding for which all those interested in the history of mediaeval thought, particularly of that vital period the Renaissance, will be grateful.

K. D. KEELE.

PREPAID MEDICAL CARE IN CANADA

Comprehensive Medical Services under Voluntary Health Insurance. A Study of the Windsor Medical Services. By Benjamin J. Darsky, M.A., Nathan Sinai, Dr.P.H., and Solomon J. Axelrod, M.D., M.P.H. (Pp. 392+xvii. 60s.) Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1958.

This is just the book for those in Great Britain who are thinking and talking about whether or not there is any alternative to the system used in our National Health Service. It describes with a wealth of detail and comment a prepayment health-insurance plan for a comprehensive medical service which has been running since 1939 in the metropolitan district of Windsor in the province of Ontario. In 1954 the Bureau of Public Health Economics of the School of Public Health of the University of Michigan was invited to study and evaluate the system, and the three authors of the book are members of the Bureau.

The number of people covered by the medical care plan is 191,608, which is 85% of the population. The district has 211 doctors, including 86 specialists, and 96% of all practising doctors have joined the scheme. They are paid direct by the plan organization on a fee-per-service basis. There is a long schedule of fees chargeable by general practitioners and another for specialists, but when the family income exceeds a specified amount an additional charge may be made. The scheme was initiated by the doctors themselves, and it is controlled by a board containing a majority of doctors, together with a few laymen selected by the doctors. The average net income in 1954 of doctors in full-time practice, after deducting practice expenses but before tax, was $13,762, but the range is considerable: 6% had incomes less than $2,500, and 8% more than $25,000. In that year 60% of doctors' professional income came from the scheme, 20% from private fees, and the remaining 20% from other sources.

Membership is limited to employed groups of ten or more, and there is an income limit which, for full benefit, for a family unit is $6,500. Those not included are the self-employed, those in small businesses, the public-assistance group, and the needy aged. If the whole population is to be covered it is suggested that public funds should pay the premiums for "Government beneficiaries."

The scheme is financially sound, but the doctors' accounts are examined by a medical committee, who disallowed an average of 3.1% for visits deemed unnecessary, and all accounts are discounted by 10%; this is regarded as equivalent to what it would cost the doctors to collect fees plus the sums which, under private practice, would be bad debts. The cost of administration is just under 8% of the premium income. By our standards the premiums may be regarded as heavy. They have been increased five times since 1939, and for a man and wife are now $4.90 a month. The benefits do not include maintenance in hospital, which can be insured against separately. There are waiting periods before benefits begin, and certain exclusions such as treatment of drug addiction and acute venereal disease. Charges made by a doctor for treating a patient in hospital are covered, except for mental patients and the tuberculous. Patients have to pay their bills for drugs and appliances. The average annual number of services received by the patients was 4.2. They ranged from none in 32% of the members to 92 items in the year.

The vast majority of both patients and doctors are satisfied with the medical-care plan. There have been difficulties, but they appear to have been straightened out as they arose. The special features are payment on a fee-per-service basis, free choice of doctor, and medical society sponsorship. Whether or not a similar scheme would work elsewhere is anybody's guess, but it quite clearly works in the place of its birth.

ALLEN DALEY.

PERIPHERAL NERVE INJURIES

Peripheral Nerve Injuries. By Ruth E. M. Bowden, D.Sc., M.B., B.S., L.R.C.P., M.R.C.S. (Pp. 62+viii; illustrated. 8s. 6d.) London: H. K. Lewis and Co., Ltd. 1958.

It is no mean feat to condense into a book of 62 pages a clear, concise, and up-to-date account of peripheral nerve injuries. But Professor Bowden has achieved this, and is to be warmly congratulated. The varieties of nerve damage are explained and classified, and methods of examination and diagnosis are described together with a simple account of anatomy. Treatment is outlined and the value of mobility and of supporting splints emphasized. Suggestions are made for further reading. The book is profusely illustrated with very clear drawings. This book will be of value not only to students, residents, and physiotherapists, but also to general surgeons whose work may only occasionally include a case of peripheral nerve injury. It should certainly be in the library of every medical college and of every hospital.

D. W. C. NORTHFIELD.

PRACTICAL MICROSCOPY

The Practical Use of the Microscope, including Photomicrography. By George Herbert Needham, M.S., F.R.M.S. (Pp. 493+xxiv; illustrated. £5 17s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Great progress has been made in microscopy during the last 20 years, and a modern textbook is certainly needed. Unfortunately this book is marred by a number of very serious defects. The writing is often loose, unscientific, and misleading, as the following quotations from the glossary will show: "Refractive index. A relationship between the sine of the angle of incidence and the sine of the angle of refraction when a ray of light passes from air to a transparent medium." "A wavelength of light is the distance between like phases of the ray." "Cardioid. A dark field condenser with two reflecting surfaces (the first is spherical, the second is a cardioid)." The remarkable statement is made that "there is no connexion between the focal length of an objective and its working distance, except that they are directly proportional." Unfortunately these are by no means isolated examples.

Another serious criticism is that the sections dealing with special methods, such as phase-contrast, ultra-violet, and electron microscopy, are extremely weak and mostly out of date. Only two of the 36 references quoted on phase contrast are later than 1950. The most recent reference to the quartz ultra-violet microscope is 1939, and no post-war model is mentioned. Only obsolescent electron microscopes are described, and, though some space is devoted to the high-speed microtomes of 1948, modern routine thin-sectioning methods receive only a passing mention.

A great deal of work has obviously gone into this book, and it is a pity that its value has been largely lost through such faults. It requires careful rewriting, and it might be wise to eliminate the chapters on special methods, which deserve a much more thorough and scientific treatment.

ROBERT BARER.

PSYCHIATRY FOR THE G.P.

Psychiatry in General Practice. By J. A. Weijel, M.D. (Pp. 208+vii. 37s. 6d.) Amsterdam, New York, Princeton: Elsevier Publishing Company. London: D. Van Nostrand Co., Ltd. 1958.

In his introduction Dr. Weijel describes the purpose of his book as an attempt to make psychiatry available for general practice. This is an admirable objective, and the author shows considerable understanding of general practice and its problems. He is well aware of the numbers and the types of case which confront the family doctor and the difficulties many of us have in dealing with such patients. He realizes our inadequate training in this branch of medicine, and suggests that much more attention should be paid to it, especially at student level. He argues, quite rightly, that many of the cases we meet with in general practice are minor psychiatric problems, often self-limiting, and requiring no profound psychotherapy. He has accepted a good deal of the Balint approach, but he suggests that even this is too specialized for the family doctor.

The book is full of useful information and wise observations. We are told that, whereas patients have learned to undress themselves for the doctor, we never meet an "undressed psyche." The general practitioner is warned to be on the look-out for transference situations, but he should be wary about offering an interpretation. The more practical side of the book is focused round a psycho-social questionary which allows for a superficial assessment of these cases without the need to probe too deeply. It will interest family doctors who are already converted, and teachers of psychiatry, but unfortunately it will not attract the very people it is supposed to help. It is not an easy book to read, and it is loaded with jargon which will put many people off. "Psychic determinism is a part, a branch of the thesis of absolute interdependency"; "The proper psychotherapeutic field for the general practitioner is the converted, the non-identical psychotherapy." Such sentences—and there are many more—are obscure, and uninviting to the average general-practitioner reader.

C. A. H. WATTS.

The task of the many experts who contribute to the review of the year's work in the *Medical Annual* for 1959 (John Wright and Sons Ltd.; price £2 2s.) is a formidable one. From the vast number of papers and reports available they have to select for comment those likely to be of greatest interest and use to the busy clinician. That they succeed in this task so admirably is a credit to the writers themselves and to the two editors, Dr. R. Bodley Scott (who has now taken over from Sir Henry Tidy) and Professor R. Milnes Walker. The subjects selected for the five special articles in this volume are the new sex hormone preparations (progestogens), cancer research, cross-infection in the ward, emphysema, and fluid and electrolyte balance in practice. As usual the excellent illustrations, especially of surgical subjects, are a great help to the reader in following the text.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Symposium on Glaucoma. Transactions of New Orleans Academy of Ophthalmology, 1957. Editor: William B. Clark, M.D., F.A.C.S.; Associate Editor: Joe M. Carmichael, M.S.J. (Pp. 314; illustrated. £5 1s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

An Almanack for the Year of Our Lord 1960. Established 1868 by Joseph Whitaker, F.S.A. (Pp. 1,188+xxxi; illustrated. Complete edition 21s.; Shorter edition 11s. 6d.; Library edition 37s. 6d.) London: Whitaker's Almanack. 1959.

Acute Pericarditis. By David H. Spodick. (Pp. 182+x; illustrated. $6.50.) New York and London: Grune and Stratton. 1959.

Modern Trends in Accident Surgery and Medicine. Edited by Ruscoe Clarke, M.B.E., M.B., F.R.C.S.(Eng.), F. G. Badger, B.Sc., F.R.C.S.(Ed.), and Simon Sevitt, M.D., M.Sc., F.R.C.P.I., D.P.H. (Pp. 330+xi; illustrated. 75s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

Atelectasia Pulmonar. I. Conceito. II. Fisiopatologia Circulatoria. By Robalo Cordeiro. (Pp. 518+xx; illustrated.) Coimbra, Portugal: Faculdade de Medicina de Coimbra. 1959.

Effect of Small Doses of Alcohol on a Skill Resembling Driving. By G. C. Drew, W. P. Colquhoun, and Hazel A. Long. Medical Research Council Memorandum No. 38. (Pp. 108+vi; illustrated. 7s. 6d.) London: H.M. Stationery Office. 1959.

Library of the Academy of Sciences of the U.S.S.R. Guide-Book. By I. F. Grigorjeva, T. M. Kovalchuk, and T. I. Skripkina. (Pp. 110; illustrated.) Moscow, Leningrad: Academy of Sciences of the U.S.S.R. Press. 1959.

Hypnosis in Treatment. By William Moodie, M.D., F.R.C.P., D.P.M. (Pp. 168. 18s.) London: Faber and Faber. 1959.

Carcinogenesis by Ultraviolet Light. An Essay in Quantitative Biology. By Harold F. Blum. (Pp. 340+xv; illustrated. 52s.) Princeton, N.J.: University Press. London: Oxford University Press. 1959.

Your Health and Your Wealth. By a Doctor. (Pp. 139+vi; illustrated. 7s. 6d.) Bristol: John Wright and Sons, Ltd. 1959.

Faces, Figures and Feelings. A Cosmetic Plastic Surgeon Speaks. By Leslie E. Gardiner, F.I.C.S., M.R.C.S., L.R.C.P., D.L.O. (Pp. 176; illustrated. 18s.) London: Robert Hale, Ltd. 1959.

The Hospitals Year Book 1960. Editor: J. F. Milne, *M.C.*, B.Sc.(Econ.). Advisory Editor: S. R. Spiller, O.B.E., LL.B. (Pp. 1,167+vii. 59s. 6d.) London: Institute of Hospital Administrators. 1959.

Communicable Diseases in Schools: A Survey of Existing Legislation. (Pp. 66. 3s. 6d.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Bulletin of the World Health Organization. Vol. 21, No. 1. ***Tuberculosis: Epidemiological Basis of Tuberculosis Eradication in Denmark. A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India.*** (Pp. 144; illustrated. 10s.) Geneva: World Health Organization. London: H.M. Stationery Office. 1959.

Some Guide Lines for Evaluative Research: Assessing Psychosocial Change in Individuals. By Elizabeth Herzog. (Pp. 117. 35c.) Washington, D.C.: U.S. Department of Health, Education and Welfare. 1959.

At Your Best for Birth (and Afterwards). By Eileen Montgomery, M.C.S.P. (Pp. 59; illustrated. 5s. 6d.) Bristol: John Wright and Sons, Ltd. 1959.

Handbuch der Berufskrankheiten. By Dr. Franz Koelsch. Second edition. (Pp. 1,134+xi. DM. 76.) Jena: VEB Gustav Fischer Verlag. 1959.

Love in Action. The Sociology of Sex. By Fernando Henriques, M.A., D.Phil.(Oxon.). (Pp. 432; illustrated. 45s.) London: Macgibbon and Kee. 1959.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P. Sixth edition. (Pp. 751+xii; illustrated. 45s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Milk Testing. The Laboratory Control of Milk. By J. G. Davis, D.Sc., Ph.D.(Lond.), F.R.I.C., M.I.Biol., F.R.S.H. Second edition. (Pp. 309+xiv; illustrated 30s.) London: Dairy Industries, Ltd. 1959.

BRITISH MEDICAL JOURNAL

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CULTIVATION OF THE COMMON COLD VIRUS

The Common Cold Research Unit of the Medical Research Council has now been at work for 13 years. During this time over 6,000 volunteers have been received at the Harvard Hospital near Salisbury, isolated there for 10 days or so, and used as experimental animals for the study of this infection. Many of them have been inoculated with material in which the propagation of the virus *in vitro* has been attempted, and with few exceptions, in tests which failed on repetition, these attempts have been fruitless.

The patient continuation of such work seems now to have been rewarded by distinct advances in several directions, an account of which is given in a series of three contributions in this week's issue of the *Lancet*, made available to us by the courtesy of the Editor. The first of these, by D. A. J. Tyrrell, M. L. Bynoe, G. Hitchcock, H. G. Pereira, and C. H. Andrewes,[1] records more consistent success than has been achieved before in propagating the cold virus in tissue culture. In one successful earlier attempt of this kind the culture used was one of human embryonic lung. Three embryonic tissues have been tried in the present work: lung and thyroid gave negative results, but success was obtained with cultures of human embryonic kidney. Material from the first and second passages of cultures in this medium of two strains of virus produced colds in 22 out of 102 volunteers. Numerous control experiments were necessary to establish the significance of this finding: it was shown that the starting material did not contain any other known virus, and that none was contained in the constituents of the medium. Systematic variations in the technique of cultivation were then introduced in the hope of improving it: the temperature was reduced to 33° C., an extra 0.1% of glucose was added to the medium, and the interval between transfer was changed. Apparently as the result of these modifications a third strain of virus was propagated so successfully that the culture remained infective up to the eighth transfer.

It is also recorded in this paper that one of these viruses, in the form of the original washings, was rendered non-infective by exposure to acid (*p*H 2.1) and by gamma globulin, but not by treatment with ether or by convalescent serum from the donor from whom it was derived. Two of these observations are important in relation to the subject of the second paper, by Hitchcock and Tyrrell.[2] In these further experiments cultures of human embryonic kidney were inoculated with cold virus, and five days later, when the medium was renewed, further inoculated with parainfluenza virus type I or E.C.H.O. 11 virus. The degree of proliferation of these viruses was determined by haemagglutinin titration, and was found to be diminished in comparison with that in control cultures containing no cold virus. This interference by the cold virus with the growth of other viruses persisted throughout eight transfers of three out of four strains so tested. Moreover, cold virus exposed to acid as in the previous experiments no longer caused interference, but after treatment with ether it did. It was also found that the interfering agent was destroyed at 56° C., and would pass through a gradocol membrane with an average pore-size of 490 mμ.

The third paper, by Tyrrell and R. Parsons,[3] describes and illustrates cytopathic changes produced by the cold virus in tissue cultures of both human and monkey kidney cells. In order to obtain this effect the lower temperature of 33° C. was found advantageous, but a further requirement was a reduction in the bicarbonate content of the medium. It is remarked in this connexion that "these cooler and more acid conditions are like those which obtain at the surface of the nasal mucous membrane." "Rounding up" and degeneration of the cells was observed in foci which slowly extended. Again it was shown that the agent causing this effect had the same properties as the infective agent: it was destroyed by heat or acid but not by ether, and passed the same filter. It was also found to be neutralized by convalescent serum.

It has thus been shown that the same agent will not only proliferate in certain kinds of tissue culture but will interfere with the proliferation of other viruses in tissue culture and will cause cytopathic changes in such cultures. Hitherto it has been possible to prove the presence of cold virus only by the inoculation of human volunteers. It is now possible to prove its

[1] Tyrrell, D. A. J., Bynoe, M. L., Hitchcock, G., Pereira, H. G., and Andrewes, C. H., *Lancet*, 1960, **1**, 235.
[2] Hitchcock, G., and Tyrrell, D. A. J., ibid., 1960, **1**, 237.
[3] Tyrrell, D. A. J., and Parsons, R., ibid., 1960, **1**, 239.

presence by other and considerably simpler means, and it is in making these new methods available for future work that this study has scored its principal success. It is interesting that such simple modifications of the cultural technique as slight alterations of temperature and *p*H should have had such an important effect. Is it possible that further improvement might result from reduction of the antibiotic content of the medium? This contained substantial amounts of penicillin, streptomycin, and nystatin. Is enough known about the properties of this virus to provide assurance that its growth will be altogether unaffected by this formidable combination? In the past, tissue cultures have been maintained for long periods without these adventitious aids, and since the virus has been found to be filtrable, and the inoculum could therefore be bacteria-free, presumably there is no insuperable barrier to dispensing with antibiotics altogether.

There are already indications that not all cold viruses are alike: some grow in cultures of human kidney and some in those of rhesus-monkey kidney, and other apparent differences have been observed. With the much greater scope for research offered by these observations, work on the common cold will evidently receive a new impetus. Since nothing can wholly replace a test of infectivity, the need for volunteers to participate in this work becomes greater rather than less. This is emphasized in a statement issued to the press by the Medical Research Council, appealing to anyone in normal health and between 18 and 45 years of age who is willing to spend 10 days in comfortable isolation, with a "considerably less than fifty-fifty chance of catching a cold," to communicate with the Medical Superintendent, Harvard Hospital, Salisbury. This free holiday is particularly commended to students working for examinations.

AETIOLOGY OF IDIOPATHIC HYPERCALCAEMIA

Idiopathic hypercalcaemia has been a subject of research since 1952, when the so-called mild or benign form of the disease was first described by R. Lightwood.[1] Though most cases end in complete recovery, the illness is unpleasant and lasts some months. In the severe form of the disease[2 3] the brain, kidneys, heart, and bones suffer irreversible damage. It was at first thought that these were two separate syndromes,[4 5] but the subsequent appearance of intermediate cases suggests that they may represent only different degrees of severity.[6]

The apparent similarity of idiopathic hypercalcaemia to intoxication with vitamin D suggested that it might be related to the modern practice of fortifying dried milks and cereals with calciferol (vitamin D_2). Some infants suffering from idiopathic hypercalcaemia had received as much as 4,000 units of vitamin D each day. In several patients calcium-balance studies showed that an abnormally high proportion of the dietary calcium was absorbed.[7–9] Vitamin D has the distinctive property of increasing the absorption of calcium from the gut, and cow's milk—invariably the diet of these affected infants—contains about four times as much calcium as human milk. On the other hand, most infants would not be upset by these doses of vitamin D, and the amounts given to some babies with idiopathic hypercalcaemia have been small. It was therefore suggested that the infants affected by this disease might have an undue sensitivity to vitamin D.[5] R. E. Bonham Carter and his colleagues[10] gave one infant with the mild form of the disease in a state of remission 10,000 units of calciferol daily for 10 days. This was followed by an exacerbation of the disease and a rise in the plasma levels of calcium and urea. They concluded that the patient was hypersensitive to vitamin D. W. M. Fyfe[11] found that in affected infants the vitamin-A levels in the blood, when fasting and four hours after a standard dose of vitamin A, were significantly higher than in healthy infants or in infants marasmic from other causes.

Since both vitamins A and D are fat-soluble, an abnormal metabolism of vitamin A suggests the possibility of an abnormal disposal of vitamin D. J. O. Forfar and his colleagues[9] made detailed chemical studies in six cases of the mild form of hypercalcaemia of infancy, and interpreted the results as showing that, though vitamin D seemed to have some effect, neither excessive ingestion of it nor specific hypersensitivity to it could explain all the features. Thus, administration of calciferol in daily doses of 50,000–100,000 units to two patients did not

[1] Lightwood, R., *Proc. roy. Soc. Med.*, 1952, **45**, 401.
[2] Fanconi, G., and Girardet, P., *Helv. paediat. Acta*, 1952, **7**, 314.
[3] Schlesinger, B. E., Butler, N. R., and Black, J. A., ibid., 1952, **7**, 335.
[4] Lightwood, R., and Stapleton, T., *Lancet*, 1953, **2**, 255.
[5] Lowe, K. G., Henderson, J. L., Park, W. W., and McGreal, D. A., ibid., 1954, **2**, 101.
[6] Joseph, M. C., and Parrot, D., *Arch. Dis. Childh.*, 1958, **33**, 385.
[7] Creery, R. D. G., and Neill, D. W., *Lancet*, 1954, **2**, 110.
[8] Morgan, H. G., Mitchell, R. G., Stowers, J. M., and Thomson, J., ibid., 1956, **1**, 925.
[9] Forfar, J. O., Balf, C. L., Maxwell, G. M., and Tompsett, S. L., ibid., 1956, **1**, 981.
[10] Bonham Carter, R. E., Dent, C. E., Fowler, D. I., and Harper, C. M., *Arch. Dis. Childh.*, 1955, **30**, 399.
[11] Fyfe, W. M., *Lancet*, 1956, **1**, 610.
[12] Fellers, F. X., and Schwartz, R., *New Engl. J. Med.*, 1958, **259**, 1050.
[13] Salt, H. B., and Wolff, O. H., *Arch. Dis. Childh.*, 1957, **32**, 404.
[14] Report of the Joint Subcommittee on Welfare Foods, 1957, H.M.S.O. London.
[15] *Brit. med. J.*, 1957, **2**, 284.

cause significant clinical or chemical deterioration. The high retention of phosphorus in these cases, as well as of calcium, was not in keeping with vitamin-D overactivity, nor was the hypophosphaturia. Low levels of citrate in the serum and urine in three cases gave no indication of increased vitamin-D effect, in which raised values may be obtained. On the other hand, Forfar and colleagues[9] noted in their own and other published cases some degree of hypercholesterolaemia, and a significant positive correlation between serum levels of calcium and of cholesterol. The ratio of free cholesterol to cholesterol-ester tended to be high, as did the ratio of cholesterol attached to β-lipoprotein compared with that attached to α-lipoprotein. They suggested that cholesterol metabolism is disordered in this disease, and that cholesterol derivatives with a vitamin-D-like effect as well as other toxic effects are produced in excess. It is indeed well known that some sterols have antirachitic as well as toxic properties—for example, toxisterol.

Recently F. X. Fellers and R. Schwartz,[12] of the Harvard Medical School, reported the results of intensive metabolic studies in three infants with the severe form of the disease. Cholesterol levels were raised in two patients. All showed abnormally high levels of vitamin A, and in two the serum level of citrate was increased. Hypercalciuria was found in all three infants, urinary citrate was reduced, and the excretion of organic acid was normal. Glomerular filtration, renal plasma flow, and tubular secretory function were depressed. Excessive amino-aciduria was not found. Excessive calcium was retained in the body. Of particular interest were the levels of vitamin D in the serum as determined by bioassay when compared with the levels in four normal infants. The serum levels in the normal infants varied from 100 to 600 units per 100 ml., whereas in the three hypercalcaemic infants the serum contained 1,700 to 6,000 units per 100 ml. In a child with resistant rickets who was receiving 62,500 units of vitamin D daily the serum level was 4,300 units per 100 ml. As Fellers and Schwartz point out, the previous daily intake of vitamin D by their three patients (up to 1,500 units) would not be expected to produce such high vitamin-D activity in the serum. Furthermore, such levels were found as long as 14 months after removal of vitamin D from the diet. This is well beyond the period during which exogenous vitamin might persist in normal people. They suggest that the high vitamin-D activity in the serum of their patients is not the naturally occurring vitamin D_3 but another sterol with antirachitic properties. They further suggest that the abnormal distribution of lipoprotein in one of their cases, and the high lipoprotein reported in two cases by H. B. Salt and O. H. Wolff,[13] indicate the possibility of a defect in the transport of this vitamin-D-like substance. Their hypothesis is thus similar to that put forward by Forfar and his co-workers.[9] It may be, in fact, that quite small doses of vitamin D_2 can produce hypercalcaemia only in those infants who already have as the primary aetiological factor an inborn defect or error in the metabolism of vitamin D.

In 1957 the Medical Research Council Conference on Hypercalcaemia advised that a daily intake of 400 units of vitamin D was adequate throughout infancy. Subsequently the Cohen Committee[14 15] advised that the levels of vitamin D in national cod-liver oil, national dried milk, and infant cereals be considerably reduced. Although no figures are available, many paediatricians feel that the incidence of the disease has fallen since these recommendations were carried out.

BATHING IN SEWAGE-POLLUTED WATERS

The greatly increased population of British seaside resorts, particularly in the summer, has resulted in the discharge into the sea of a much greater quantity of sewage. Whatever risk to health this may entail to bathers is thus being intensified, and an inquiry into the extent of this risk was evidently advisable. This was begun in 1953 by a committee of the Public Health Laboratory Service, and its findings have now been published both *in extenso*[1] and as a memorandum[2] from the Medical Research Council, which appears to have been composed mainly for the benefit of non-medical readers. Both publications review existing information on the subject and make it clear that except in a few special instances diseases such as enteric fever have not been shown to be due to bathing in sea water.

The main task of the committee was to examine bacteriologically large numbers of samples of sea water collected on over 40 different beaches. None of these is named; it is said to have been "naturally" a condition of co-operation by local health authorities that the geographical anonymity of the sites where specimens were collected should be preserved. Valuable work was done in adapting the

[1] *J. Hyg.*, 1959, **57**, 435.

[2] *Sewage Contamination of Bathing Beaches in England and Wales*. Medical Research Council Memorandum No. 37, 1959. H.M.S.O., London. Price 2s. 6d. net.

[3] McCullough, N. R., and Eisele, C. W., *J. infect Dis.*, 1951, **88**, 278, and **89**, 209, 259.

methods used in examining fresh-water supplies to this very different purpose—different because the numbers of bacteria to be enumerated were enormously larger. It was shown that the total coliform count bore a fairly constant relation to the faecal coli content and, indeed, to the frequency with which actual pathogens could be isolated. For comparison with these findings it should be remembered that a good water from a public supply should contain no coli in 100 ml., and that (to quote this memorandum) "when sewage contamination of city water supplies occurs, even to the extent of showing coliform counts of say 20 per 100 ml., extensive water-borne disease often results." Many samples of sea water examined contained thousands of coliforms per 100 ml., and counts even of over 100,000 are recorded. On beach "D" the median coliform count in 348 samples was 24,000 and the median faecal coli count was 7,000. Moreover, from 40% of samples with a coliform count of over 10,000, and somewhat lesser numbers of those with lower counts, pathogenic organisms of the *Salmonella* group could be isolated, some being *Salm. paratyphi B*, the remainder *Salm. typhi-murium* and various others of the food-poisoning group. These were recovered from 1- or 3-litre samples by the highly selective methods available for this genus, and evidence was obtained that they were present only in small numbers.

The coliform counts from a given beach varied very widely at different times: wind force and direction and tidal movements were largely responsible for this, and the effect of other factors was also studied. The committee therefore came to the conclusion that a bacteriological standard for sea water is impracticable. Such standards have been established at various levels of coliform count by local health authorities in the United States, but there is no single agreed standard. If it is necessary to examine many samples obtained under different tidal and climatic conditions to obtain a representative picture of the state of a beach, the committee's conclusion seems inevitable, although there might well be a case for condemning a beach giving an exceedingly high coliform count under any such conditions. The further conclusion reached by the committee is very reassuring, particularly to the health authorities of seaside resorts, but may seem somewhat tinged with optimism. It is that "bathing in sewage-polluted sea water carries only a negligible risk to health, even on beaches that are aesthetically very unsatisfactory," and that "with the possible exception of a few aesthetically revolting beaches . . . the risk to health of bathing in sewage-contaminated sea-water can, for all practical purposes, be ignored." It is also suggested that "the minimal risk attending such bathing is probably associated with chance contact with intact aggregates of faecal material. . . ." Whether mere contact with the skin is meant or whether it is implied that solid faeces must enter the mouth is not clear.

This comforting conclusion is based in part on epidemiological studies and in part on a theoretical argument. The former were inquiries into the bathing history of patients who had had poliomyelitis and enteric fever. No association of bathing with the former was revealed, and only four cases of paratyphoid fever in 1956–8 could be attributed to bathing, one on the notorious beach "D" already referred to and three on beach "J," apparently similar but in fact missing from the table said to record its degree of pollution. The general statement is also made that enteric fever is not unusually common in seaside residents, and it is pointed out that only 310 cases of paratyphoid fever were notified in England and Wales in 1957. The theoretical argument is that disease is caused only when such bacilli are swallowed in large numbers. This doctrine is based on the fact that in epidemics of paratyphoid the vehicle is often a food, such as milk or artificial cream, in which multiplication can occur, and on the experiments of N. R. McCullough and C. W. Eisele,[3] who administered different doses of cultures of various salmonellas to human volunteers. The source of these cultures (dried egg) may have had some bearing on their virulence for man, and the vehicle was "egg-nog": if this contained enough brandy to commend it to the Chicago prisoners who were the subjects of this experiment, there seems a possibility that not all the bacilli survived in it.

The main justification for the committee's conclusions is simply this: that in view of the heavy pollution demonstrated on certain beaches bathing there could cause a great deal of disease, but in fact it does not. Presumably these beaches are used by many bathers, although on this no information is given. Even allowing for the fact that many sporadic cases of salmonella enteritis probably escape detection, the risk is evidently small. Yet how many ordinarily careful and fastidious people would take it with these findings in mind and if instructed about their significance? A pronouncement by the Medical Research Council condoning such grossly insanitary conditions makes strange reading.

DEPOT TUBERCULIN AND DEPOT LEPROMIN

In order to exploit the enhanced potency and prolonged local persistence of depot tuberculin, special preparations are required. The liquid-paraffin–lanolin vehicle originally used for the preparation of an emulsion of depot tuberculin was unsatisfactory for general use because the vehicle itself was irritant.[1] Some advance with more suitable preparations can now be recorded.[2] The purified protein derivative of tuberculin, P.P.D., was incorporated in a wool-alcohol cream ("eucerin"), which was then introduced into the skin by multiple puncture with the Heaf apparatus. In spite of considerable enhancement of the potency of the tuberculin in this test preparation, reactions to it were only of mild intensity, though of prolonged duration. Positive results with depot P.P.D. tests were elicited in a high proportion of subjects who failed to react to Mantoux tests with 100 T.U. (tuberculin units). In a group of 32 nurses aged 18 years, 40% reacted to Mantoux tests up to 100 T.U., whereas 90% reacted to the depot P.P.D. test. In 489 factory workers aged 17–55 years, 83% reacted to Mantoux tests up to 100 T.U. and 92% to the depot P.P.D. test. The immunological significance of the positive depot P.P.D. tests in Mantoux-negative subjects was shown by the accelerated reactions which appeared in response to the injection of full doses of B.C.G. vaccine in 14 out of 15 subjects. Such accelerated reactions to B.C.G. in Mantoux-negative subjects have been termed infra-tuberculin allergy.[3] They remain unexplained so far.

The appearance of reactions to depot P.P.D. tests in tuberculous patients who had been desensitized to tuberculin and failed to react to Mantoux tests with concentrated old tuberculin, equivalent to a test dose of 10,000 tuberculin units, illustrates the high potency of this preparation. Reactions to depot P.P.D. cream tests have also been produced in Mantoux-negative patients with sarcoidosis.

A group of 32 subjects who failed to react to either Mantoux or depot P.P.D. tests were vaccinated with B.C.G. In all of them positive reactions appeared at the depot test sites within six weeks of the vaccination, indicating conversion to tuberculin sensitivity and illustrating the prolonged retention of the depot P.P.D. at the test sites.

Similar investigations have been reported with a depot lepromin, prepared as a cream in an emulsion of liquid paraffin and lanolin for multiple puncture tests.[4] Complete agreement was obtained in the reactions to the depot lepromin and to the conventional intracutaneous lepromin test in tuberculoid and lepromatous cases of leprosy. The depot lepromin seems to be more potent than, and is economical of, aqueous lepromin, a relatively scarce material, since 1,000 patients can be tested with 1 ml. of lepromin incorporated in the emulsion, as against 10 patients for whom 1 ml. is needed for intracutaneous tests. Though the potency of the lepromin was enhanced in the depot preparations, it did not excite reactions in lepromatous subjects who gave the usual negative reactions to aqueous lepromin.

A group of 18 healthy children with negative reactions to tuberculin and to depot lepromin were vaccinated with B.C.G.[5] Reactions appeared at the previously negative depot-lepromin sites three to six weeks after the B.C.G. vaccination, thus indicating that the B.C.G. antigens responsible for the production of tuberculin hypersensitivity are antigenically related to *Mycobacterium leprae*. In lepromatous lepers who give negative reactions to lepromin and to tuberculin, it is recognized that B.C.G. vaccination produces conversion to tuberculin sensitivity but does not produce lepromin sensitivity. While this suggests that B.C.G. vaccination may be applicable rather more to prophylaxis in healthy subjects than to treatment of lepromatous lepers, further investigations are needed. Sensitization during the period of observation by the depot lepromin test itself did not seem likely, since an interval of 11 weeks elapsed between depot lepromin tests performed five weeks before vaccination and the appearance of reactions at the depot-test sites six weeks after the B.C.G. vaccination.

The enhanced potency, simplicity, and economy of the depot preparations appear advantageous. Before accepting them for general use a number of pertinent questions requiring large-scale field studies for their answer present themselves. For example, what is the incidence, if any, of sensitization produced by the depot test itself to tuberculin, lepromin, or the vehicle constituents? What is the influence of the depot test on existing tuberculin sensitivity? What is the significance of the very low degrees of tuberculin hypersensitivity shown by the depot tests? The question whether the very low degrees of hypersensitivity are associated with protection can be answered only by observations under controlled conditions of the susceptibility of such subjects to tuberculosis. Finally, it remains to be seen whether and for how long the depot P.P.D. can persist in the skin of negative reactors so as to reveal the subsequent development of hypersensitivity in response to active infection.

[1] James, D. G., and Pepys, J., *Lancet*, 1956, **1**, 602.
[2] Pepys, J., Bruce, R. A., and James, D. G., *Tubercle* (*Lond.*), 1958, **39**, 283.
[3] De Assis, A., and Carvalho, A. de, *Hospital* (*Rio de J.*), 1942, **22**, 173.
[4] Brown, J. A. K., *Leprosy Rev.*, 1958, **29**, 184.
[5] —— and Stone, M. M., ibid., 1959, **30**, 110.

PLACENTA ACCRETA

When delayed or incomplete separation of the placenta complicates the third stage of labour, there is usually no anatomical abnormality of the placental attachment. Rarely, however, there is a condition known as placenta accreta. This is a pathological adhesion of the placenta to the uterine wall, so that when manual removal is attempted no plane of cleavage is found. In a recent clinico-pathological study of 14 cases of placenta accreta, W. G. Millar[1] has illustrated in excellent fashion the absence, or very poor development, of the decidua, which is the basic histological feature; at the placental site there is also hyalinization of the immediately subjacent myometrium. The villi are attached directly to the uterine muscle or a layer of fibrin may intervene, but variations in the chorionic plate and distribution of fibrin are within the normal range. In about half of

the cases the villi penetrate deeply into the muscle (placenta increta), but it is rare for them to extend to the peritoneal coat (placenta percreta). The abnormality in this last degree may lead to spontaneous rupture or perforation of the uterus, but these are more likely to be caused by the hand of the obstetrician in his forceful attempts at separation.

Dr. Millar's belief that the decidual deficiency is primary, and not secondary to absorption of the initially normal decidua, is supported by the finding of accretion as early as the tenth week of pregnancy. Such an occurrence may indeed explain why the surgical completion of an incomplete miscarriage or evacuation of a missed abortion is sometimes difficult and bloody. Two other findings support the view that the decidual deficiency is primary. In about 20% of cases of accretion the placenta is also of the membranaceous type, the larger area of which is generally held to be a reaction to poor decidual production. And in another 20% the placenta accreta is also praevia—that is, implanted on the lower segment, where the decidual reaction is normally weaker than in the upper segment.

Clinically, accretion of the placenta is usually discovered only when manual removal is attempted. In the two-thirds of cases in which the accretion is partial or incomplete, the operation will have been essayed because of third-stage bleeding. The accoucheur must desist from attempting detachment where there is no plane of cleavage, but maintain the general condition of the patient until hysterectomy can be performed. However, if the whole placenta is pathologically adherent, there can be no bleeding from the placental site. In such a case, once the woman is in hospital, conservative management may be preferred, the placenta being left *in situ* with the cord cut short, antibiotic cover being given for some days, and blood being held ready for transfusion should any secondary post-partum haemorrhage occur. Such conservative treatment has gained in popularity since 1940, when E. A. Schumann[2] reported that two women so treated had later become pregnant again.

The cause of the decidual deficiency in placenta accreta is not known. The predisposing effects of previous local infection or trauma, including caesarean-section scars, have been discounted. But the high rate of previous manual removal of the placenta in affected women—5 out of the 11 multigravidae in Millar's series—suggests that a lesser degree of decidual deficiency may occur in earlier pregnancies in these patients. Millar suggests that the cause may be hormonal, but there is not yet any strong evidence to support this view. In the meantime two intriguing questions remain. If the absence of the decidua is primary, how does the fertilized ovum obtain a first firm hold to become implanted and then nourished so that the embryo and its supports can develop normally? And in the absence of the decidual cells, which normally limit the penetration of the erosive trophoblast, why does not the placenta accreta always penetrate through to the peritoneal coat of the uterus?

[1] Millar, W. G., *J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 353.
[2] Schumann, E. A., *Med. Rec.*, 1940, **151**, 381.

ARTIFICIAL INSEMINATION BY DONOR

About eighteen months ago a departmental committee was set up by the Government to inquire into artificial insemination. The memorandum of evidence[1] submitted by the British Medical Association to the committee on the medical aspects of the subject was published last summer. Two further memoranda[2] to the committee were published last week: described as "contributions to a Christian judgment," the first was from the Archbishop of Canterbury and the second from a small committee (including one medical member) appointed by the Archbishop to prepare the Church of England's evidence. The committee felt it had not much to add to the findings of the Archbishop of Canterbury's commission[3] on artificial insemination which reported twelve years ago. Like the commission, the committee found that insemination of the wife with her husband's semen may be justified. As to A.I.D., the committee held that this was "wrong on theological, moral, and social grounds," and therefore recommended that there should be legislation declaring that the practice of A.I.D. was on the same footing as adultery or fornication. As a consequence of such a clarification of the law the committee hopes that:

> "The General Medical Council will regard it as unprofessional conduct for a medical practitioner to assist in the practice of A.I.D. If . . . this should result in the withholding of virtually all medical assistance in the practice of A.I.D., we think it improbable that that practice will ever assume sinister proportions."

Should A.I.D. ever come to be regarded as perfectly lawful, then, in the committee's view, the practice should be regulated—not by the operation of the law, but "from the influence or control of the appropriate medical authority over its own members," and in this connexion the Royal College of Obstetricians and Gynaecologists is specifically mentioned.

The Archbishop of Canterbury's memorandum of evidence discusses the medical, legal, social, and Christian aspects of the subject. So far as the merits of A.I.D. are concerned, Dr. Fisher points out that the B.M.A.'s evidence gave little support on medical grounds to the continuance of the practice, and adds that there is a substantial body of opinion in the profession which regards the practice as an undesirable one. The ordinary citizen's objection to A.I.D. is, in Dr. Fisher's view, partly a dislike of admitting doctors and donors into the most intimate affairs of husband and wife. In A.I.D. the doctor arrogates to himself a creative function which has throughout human history belonged exclusively to a man and a woman through personal sexual intercourse. Dr. Fisher feels that eventually this might have an adverse effect on the relation, pastoral as well as medical, between the doctor and society.

The Archbishop's memorandum concludes that there is general agreement that A.I.D. must be either forbidden or brought under legislative control. For his own part he wishes to see the practice prohibited by law.

[1] *Brit. med. J., Suppl.*, 1959, **1**, 289.
[2] *Artificial Insemination by Donor*. Published by the Church Information Service, Church House, Westminster, S.W.1. Price 2s.
[3] See annotation, *Brit. med. J.*, 1948, **2**, 523.

Drug Treatment of Disease

DRUGS FOR MENOPAUSAL SYMPTOMS

BY

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The symptoms in question are ill-named "menopausal" and are better termed "climacteric." They result from the cessation of the endocrine function of the ovary. As ovarian activity wanes the first effect is amenorrhoea, sometimes preceded by a diminution in the amount and frequency of the flow. The *first* symptom of the climacteric is therefore the menopause, and any symptoms which precede amenorrhoea are never "menopausal." This, unfortunately, is often not recognized, and many women in their 40s are led to believe that their various minor discomforts and emotional disturbances are attributable to the "change of life," even five to ten years before their menstrual function ceases. Not only do general manifestations of the climacteric never appear before the menopause but their onset may be deferred for months or years after menstruation has stopped. This is because some degree of ovarian function, insufficient to cause a menstrual flow, may continue for a variable period of time.

The ill-defined physical and psychological disorders which are common in middle age, and for which the climacteric is wrongly blamed, can usually be traced to environmental causes. Children are often at an age when they can cause parental anxiety and expense. Household duties are heavy and the mother is no longer so physically fit to cope with them. The daily round is tedious, holidays and recreations are few. On the other hand, when the children mature and leave home the mother may be left without any self-satisfying interests and lives a bored and aimless existence. Again, many women live in fear of the menopause, having heard tell of its torments and possibly having already been advised that their complaints are a sign of its approach. Among other things they fear that the change of life is an end of life, especially of sexual life. They fear loss of looks and figure, and of their husband's affection. They fear cancer, insanity, and other serious illnesses which they think have some direct association with the menopause.

Such factors and fears can not only cause symptoms which may be mistaken for those of the climacteric but they make genuine manifestations worse. The climacteric is to be regarded as a physiological test of personality. Hot flushes, for example, are more troublesome when the patient is anxious, tense, or otherwise emotionally disturbed.

True climacteric symptoms are various, but the most common are hot flushes, night sweats, cold shivers, nervousness, insomnia, depression, irritability, fatigue, and palpitation. Irregular or heavy uterine bleeding, however, is *never* a manifestation of the menopause. Such a happening cannot be caused by a cessation of ovarian function and should never be treated symptomatically. It requires complete investigation, often including curettage and cervical biopsy, to find its cause before its treatment can be determined.

GENERAL TREATMENT

Although 75% of women experience climacteric symptoms of some degree, relatively few need to seek medical advice. When they do the attendant's object should be to avoid administering drugs of any kind. Most patients require nothing more than to understand that the disturbances are physiological, temporary, and of less account if viewed philosophically, that sexual capacity need not be impaired, and that a full and active life is not at an end.

The increase in weight which is common in middle age, though not directly related to the climacteric, can always be controlled by a strict reduction of the calorific intake. Dieting to retain or restore a good figure is good for morale. The discipline is self-satisfying, and the result enables a woman to continue to dress smartly and to enjoy social engagements. She thus faces life with a confidence which helps her to discount climacteric upsets.

Many women are embarrassed not so much by their own sensation of hot flushes as by the idea that others notice the facial colour. Such patients can be assured that onlookers are not so observant as they suppose. In any case, the number and intensity of flushes can be reduced by the avoidance of hot baths, hot atmospheres, alcohol, coffee, and highly seasoned foods.

By explanation, advice, and reassurance, climacteric symptoms can be alleviated if not prevented completely. Moreover, most women prefer to have understanding than to take pills. There remains only a small minority (approximately 5%) of women, mostly those who by nature are emotional and over-anxious, for whom some form of medical treatment is necessary. The choice of drug then depends to some extent on the type of the symptoms present.

TREATMENT WITH DRUGS

Sedatives and Tranquillizers

These may be indicated for irritability and emotional upset. They may also help in quieting vasomotor instability and in reducing the number of hot flushes. It is doubtful whether there is now any better sedative for these purposes than phenobarbitone, ½ gr. (32 mg.) once or twice daily. If this is combined with ascorbic acid and vitamin-B complex, its possible depressant effect is said to be reduced, though the evidence is equivocal. Of the many tranquillizers now available, promethazine, 10 to 25 mg. each night, or meprobamate, 400–800 mg. at night, are probably as good as any for climacteric symptoms.

Stimulants

When lethargy and nervous depression are dominant symptoms, sedatives are to be avoided. Instead, amphetamine or dextro-amphetamine sulphate, 5–10 mg. twice daily, may be helpful.

Sex Hormones

Climacteric symptoms are primarily caused by a persistent fall in the production of oestrogens by the ovary. This in turn releases the anterior pituitary from an inhibition so that it pours out large amounts of

gonadotrophin. It is commonly believed that it is this secondary reaction which is directly responsible for symptoms and that this explains why the administration of either oestrogen or androgen, both of which inhibit pituitary activity, gives relief.

Oestrogens

Disadvantages

Although the administration of oestrogen offers immediate and dramatic benefit to the sufferer from climacteric symptoms, it should be adopted only as a last resort because:

(i) It is a form of substitution therapy which, when withdrawn, results in the recurrence of symptoms which may be even more severe than before treatment was given.

(ii) Though this disadvantage can to some extent be overcome by careful regulation of the dose and by gradual withdrawal of the hormone, any patient who has experienced the relief which oestrogens bring is loath to abandon them. She tends therefore to continue with treatment over long periods of time and often haphazardly. This can cause tolerance to oestrogen, demands for higher dosage, and the persistence of symptoms.

(iii) Oestrogens cause hyperplasia of the endometrium and stimulate certain epithelial elements of the breast. They also induce uterine haemorrhage, sometimes during, and sometimes after, treatment. This haemorrhage can be heavy but, in any amount, always raises the question of a new and possibly unconnected development such as carcinoma of the uterus. The patient and attendant then have this worry, and it may even become necessary to carry out curettage and cervical biopsy before a cause for haemorrhage other than oestrogen therapy can be excluded.

In women previously subjected to hysterectomy this particular objection to oestrogens no longer applies. Even so, this type of hormone therapy should not be given if the indication for the hysterectomy was either pelvic endometriosis or genital cancer. The treatment may reawaken any remaining lesions of this type.

Principles of Treatment

In view of these considerations, the method of administering oestrogens is important. The object should be to give only enough to improve symptoms—to make them tolerable, not to eliminate them. The required dose varies from one woman to another and can be determined only by trial, the index being the number of hot flushes. The aim is to reduce these to an average of 4 in 24 hours. This can be achieved within a matter of a few days, and the dose is then maintained at that level for two weeks only. Thereafter it is gradually reduced during the course of the next two to three months. At the end of that time oestrogen therapy should be discontinued completely and should not be reinstated even though symptoms recur. Many authorities apply treatment intermittently, insisting on a break of seven days every three weeks, hoping thereby to avoid endometrial hyperplasia. Be this as it may, gradual weaning is essential to success. The idea is to substitute a gradual oestrogen deprival for the sudden one which Nature, or the surgeon, may have inflicted.

At no time should the hormone be prescribed in such a form that its effects are beyond control.

Types of Oestrogen: Routes of Administration

(i) *Oral Preparations.*—The most commonly used oestrogens are the synthetic compounds stilboestrol (diethyl stilboestrol) and ethinyl oestradiol. Both are cheap and highly potent. A suitable test dose of stilboestrol is 0.1 mg. two or three times daily; it is rarely necessary to give more than a total of 0.5 mg. in 24 hours, and a daily dose of 1 mg. should never be exceeded. This last amount induces uterine bleeding in one-third of post-menopausal women. Ethinyl oestradiol is approximately 20 times more powerful than stilboestrol and not more than 0.05 mg. daily should be given. Indeed, it is best to give tablets of 0.01 mg. once, twice, or thrice daily. Synthetic oestrogens, and especially stilboestrol, sometimes cause nausea and vomiting. It may then become necessary to turn to a natural oestrogen such as oestrone and its esters. These are less potent, which is an advantage so far as climacteric symptoms are concerned, but they are expensive. The most active oral preparation is probably one of conjugated oestrogens (mostly oestrone sulphate) obtained from mare's urine. This is approximately half as potent as stilboestrol but the initial dose (as of any oestrone ester) should not exceed 1 mg. daily. This is best divided into two or three doses equally spaced.

One of the newer synthetic oestrogens, chlorotrianisene, is said to have a special tendency to be stored in subcutaneous fat. It is given with the object of building up a depot from which oestrogen is slowly absorbed in gradually decreasing amounts over the course of weeks or months. To this end the patient is given one capsule of 12 mg. twice daily for 30 days, it being essential to complete the full course irrespective of initial response. At the end of that time symptoms should be relieved and subsequent weaning is automatic. In fact flushes sometimes return in one or two weeks. Freedom from the need to keep the patient under observation, and to regulate the dose, makes chlorotrianisene at first appear very attractive. It is, however, expensive, and, despite claims to the contrary, is not free from the risk of inducing uterine haemorrhage. If the uterus does bleed, then, with the establishment of a depot, the situation becomes beyond control. If used at all, chlorotrianisene should be given only to women without a uterus.

In the search for an oestrogen which is relatively free from undesirable side-effects, methallenoestril has come into prominence. It is less likely than stilboestrol to cause nausea, vomiting, endometrial hyperplasia, and uterine bleeding, but is certainly not free from these disadvantages. A suitable initial dose is one tablet of 3 mg. once or twice daily. This preparation is expensive and should therefore be reserved for those women who react unfavourably to other oestrogens.

(ii) *Preparations for Intramuscular Injection.*—It is generally unnecessary and unwise to give oestrogens by injection in the treatment of climacteric symptoms. The psychological effect is such that the patient tends to return every week for another injection and it is difficult to break this habit. An adequate oestrogen intake can nearly always be established by the oral route.

(iii) *Implants.*—The subcutaneous or subfascial implantation of tablets of 50 to 100 mg. oestradiol is useful in selected cases in which relatively young women have to be subjected to total hysterectomy with removal of both ovaries. It provides a depot from which absorption takes place in a gradually decreasing amount over a period of 2 to 6 months. Progressive and slow deprivation of oestrogen is assured, and the symptoms of the surgical climacteric are avoided or mollified. Such treatment should never be applied to a woman with a uterus. The amount of stimulation of the endometrium is unpredictable and, if bleeding occurs, the pellet cannot usually be recovered.

Androgens

Because androgens inhibit the gonadotrophic function of the anterior pituitary they are sometimes used in the treatment of climacteric symptoms. Their main advantage is that they do not stimulate the female secondary sex organs and they cannot cause uterine bleeding. They also give a sense of well-being, eliminate depression, and increase libido. On the other hand, all the preparations are expensive, and in doses sufficient to relieve symptoms they are likely to cause hirsuties, acne,

voice changes, and other signs of virilism. The place for androgen therapy of climacteric symptoms is therefore very small, restricted possibly to those cases in which even small doses of oestrogen cause uterine haemorrhage, or in which a previous history of endometriosis or genital cancer contraindicates oestrogen therapy.

The administration of androgens follows the same principles as that of oestrogen. Having secured the patient some relief, the hormone is given in gradually decreasing amounts over the course of 2 months. Methyl testosterone is given sublingually, the initial dose not exceeding 5 mg. twice daily. Testosterone propionate is given intramuscularly, one injection of 25 mg. exerting its effect for approximately three days. Testosterone phenylpropionate or oenanthate is also given intramuscularly, one injection of approximately 50 mg. being effective for three weeks.

Newer synthetic androgenic preparations such as methyl androstenediol and methyl androstane are given sublingually in the same dosage as methyl testosterone. They are alleged to be less virilizing but are certainly not free from this effect.

Mixed Androgen and Oestrogen Preparations

There are several proprietary tablets containing both ethinyl oestradiol (in amounts varying from 0.002 to 0.01 mg.) and methyl testosterone (in amounts varying from 2.5 to 4 mg.). These are administered orally or sublingually, the initial dose being 3 to 6 tablets daily followed by a gradual reduction. Also available are preparations a single injection of which creates an intramuscular depot of 65 mg. testosterone oenanthate and 4 mg. oestradiol valerianate. This is said to produce an effect which lasts for two to four weeks.

In favour of such hormone combinations it is argued that the oestrogen prevents virilism and the androgen counteracts oestrogenic stimulation of the breasts and uterus. Both depress the overactivity of the anterior pituitary, while androgen gives a sensation of wellbeing and raises morale. Unfortunately the claims that one hormone nullifies the ill effects of the other have an insecure foundation. Preparations of this kind can certainly cause uterine bleeding on the one hand, and hirsuties on the other. They are as unsatisfactory as they are expensive. If both hormones are ever given, it is better for the medical attendant to prescribe each separately in a dose appropriate to the case.

Mixtures of Hormones and Sedatives

Certain proprietary oral preparations contain either stilboestrol or ethinyl oestradiol in combination with phenobarbitone. These, again, are to be deprecated. If both these drugs are indicated, their respective doses need to be determined and controlled independently.

Empirical Remedies

All manner of empirical remedies for climacteric symptoms have been used from time to time. Thyroid 1 gr. (65 mg.) each night has had intermittent popularity and may serve a useful purpose in certain cases. Calcium salts in doses of 30 to 60 gr. (1.9 to 3.8 g.) have their advocates; they are harmless even if their value is doubtful. More recently it was claimed that alpha-tocopherol, or dextro-alpha-tocopheryl acid succinate, will reduce the number of flushes while having no ill effects. It has to be given in doses of 200 to 1,000 mg. daily and the results are equivocal.

CONCLUSION

The climacteric is a physiological occurrence, and, even though it calls for adaptation of the endocrine and vasomotor systems to a new situation, it does so no more than does puberty. The symptoms are more trying only because they are usually faced without the optimism and faith in the future which characterizes youth. They can, therefore, nearly always be controlled by explanation, reassurance, and correction of the physical or emotional background which is making them worse. Except in a minority of carefully selected cases, there is little more justification for giving drugs (including hormones) for the flushes and tantrums of the climacteric than there is for the blushes and waywardness of adolescence.

RADIOACTIVE MATERIALS AND THE SKELETON

[FROM A SPECIAL CORRESPONDENT]

There was a busy and successful whole-day meeting of the Bone and Tooth Society at the Royal College of Surgeons on January 13, attended by many visitors. All but the first two of the ten communications were concerned with one or other aspect of the toxicity of radioactive materials which are selectively concentrated in calcified tissue.

Microtechniques for Studying Bone

Dr. P. LACROIX (Louvain, Belgium) gave a lucid and beautifully illustrated account of his work on the micro-anatomy and histochemistry of the process of calcification in the bones of puppies. The standard methods of histology and histochemistry demand the prior decalcification of tissue before sections for microscopy can be cut, but, so far as the study of calcification is concerned, this is rather like throwing the baby out with the bath-water. Nowadays, in addition, two relatively new techniques—microradiography and autoradiography with radioactive tracers like ^{45}Ca—have proved indispensable. In both techniques sections of bone, without decalcification, are cut by saw and then ground down to a uniform thickness. An *x*-ray picture of such a section, taken with soft *x* rays, and on a fine-grain emulsion so that the picture may be magnified, gives the microscopic distribution of calcium in the section, the more heavily calcified areas showing up whiter than the less heavily calcified areas which allow more *x* rays to reach the emulsion. A radioactive tracer for calcium, however, is taken up only in those areas where calcium is being actively deposited. An autoradiograph therefore picks out the sites of active calcification, and, by varying the time interval between the administration of the isotope and the taking of the specimen, an idea may be obtained of the successive changes in the sites of active calcification. One and the same section can provide an autoradiograph, a microradiograph, and, after decalcification, a soft-tissue section which can be stained to show the whereabouts of enzymes and other histochemically demonstrable substances. The three kinds of picture can be superimposed upon each other and the histochemical stages preceding active calcification precisely defined.

Many of the new observations are not yet fully understood, and, in considering the growth in width of long bones like the tibia, there was some discussion of Dr.

Lacroix's distinction between a slow process of subperiosteal bone formation and a rapid process in which new osteones fill up the spaces within a fully calcified trabecular framework.

Retention of Strontium-85 in Man

Professor G. BAUER (Malmö, Sweden) presented some results of the clinical application of a radioactive isotope of strontium, ^{85}Sr, which had been given intravenously to normal subjects, some less than 18 years old, and to patients with a variety of illnesses which affect local or general calcification of bone, mostly cases with simple fractures. This isotope emits gamma rays which can be detected with the aid of a suitable crystal and scintillation counter held close to some part of the body. The use of radioactive isotopes for clinical investigation always involves considerations of safety, and Professor Bauer said that in Sweden the maximum permissible level of exposure for workers occupationally exposed to radiation (averaged over a 13-week period) was taken as the guide to the upper limit of dosage which should be used in clinical studies of the kind he is making.

Dr. G. E. HARRISON (M.R.C. Radiobiological Research Unit, Harwell), had also used ^{85}Sr in order to learn the rate at which radioactive strontium leaves the body during the first year after its original uptake into the skeleton. Both his subjects were middle-aged scientists, and the amount of ^{85}Sr used was 50 to 100 times less than in the Swedish studies, so that a very sensitive and selective "whole-body" counter had to be used. Interestingly the whole-body counter gave somewhat inaccurate information during the first nine days after injection of ^{85}Sr—that is, while the distribution of the radioactive material in the body was changing—and the instrument had to be calibrated via measurements of the excretory loss in urine and faeces. During the first three weeks after injection 70% of the strontium left the body, but thereafter the rate of elimination greatly diminished and at the end of a year some 15% of the original dose seemed quasi-permanently fixed in the body. If these results on strontium metabolism are applied to ^{90}Sr, calculation shows that the radiation dose to the bone tissues in the first few weeks is negligible compared with the dose accumulated over the rest of the year from the chronically retained fraction of a dose.

Experimental Lesions

Experimental lesions caused by high doses of ^{90}Sr and ^{32}P, not quite large enough to kill acutely, were described in three papers. Professor M. A. RUSHTON (Guy's Hospital) described changes in the jaw and the teeth, and Dr. SHEILA MACPHERSON and Dr. MAUREEN OWEN (M.R.C. Group for Research on Bone-Seeking Isotopes, Oxford) changes in the long bones of rabbits given 600–1,000 μc./kg. ^{90}Sr. In the jaw there is a conspicuous failure of the teeth to grow, first noticeable about one month after injection, due to gross damage to the embryonic tissue at the root of the tooth. Later, tissue changes are observed, which are possibly related to the jaw tumours which develop subsequently in many of the animals. In the tibia the tissue dose was sufficient to depopulate the haemopoietic marrow and replace it by abnormal connective tissue, and the orderly process by which the cartilage columns of the epiphysial plate are converted into bone trabeculae was interfered with.

Very similar changes were illustrated in rats given ^{32}P by Dr. J. P. M. BENSTED and Dr. N. M. BLACKETT (Institute of Cancer Research, London), although in discussion Dame JANET VAUGHAN emphasized the importance of the differences between different radio-isotopes—differences in their biological behaviour as well as in their radioactive properties. Bone tumours can occur in almost all rats given sufficient ^{32}P, but there were striking differences in the frequency of bone tumours and in the time interval after which they occurred, depending on whether the dose of ^{32}P was single or divided into a number of fractions, and in the latter case on the time intervals between the doses.

Monitoring Surveys

After tea a number of survey papers were given on the radioactivity of the environment and of the normal human skeleton. Dr. F. J. BRYANT and Dr. D. H. PIERSON (Atomic Energy Research Establishment, Harwell) and Dr. R. SCOTT RUSSELL (Agricultural Research Council Radiobiology Laboratory, Wantage) gave some account of the results of monitoring human bones, air, water, and foodstuffs for ^{90}Sr, work which is co-ordinated by the Joint A.R.C./M.R.C./D.C. Management Committee on Monitoring under the chairmanship of Dr. J. F. Loutit. It is not yet clear exactly why drinking-water from lakes, rivers, or wells contains so much less ^{90}Sr than rain-water. Milk provides roughly three-quarters of the calcium in an average diet but a smaller portion of the ^{90}Sr owing to physiological discrimination by the cow. Some three-quarters of the ^{90}Sr in milk, as in cereals and vegetables like cabbage, comes from directly deposited ^{90}Sr, and only something like a quarter via uptake from the soil. If "atmospheric" contamination is no longer newly created there should therefore be a fairly rapid fall in ^{90}Sr levels to about one-quarter of what they would otherwise have been.

Professor F. W. SPIERS (Leeds) illustrated clearly the complex interrelations of physical factors and biological factors when an estimate is made of the tissue dose from the wide variety of naturally occurring radiations to which bone is subject. Radioactive fall-out contributes a few per cent. of the total. Finally, Dr. L. F. LAMERTON (Institute of Cancer Research, London), in a characteristically pungent manner, considered possible implications of this radiation dosage to bone. His paper and the subsequent discussion showed once again that the key to the problem is the mechanism or mechanisms of carcinogenesis, a fundamental problem in which work with radiation may prove peculiarly important.

ORDER OF ST. JOHN OF JERUSALEM

Those recently appointed to, or promoted in, the Most Venerable Order of the Hospital of St. John of Jerusalem include the following members of the medical profession:

As Knights: Major-General Sir Frank Kingsley Norris, K.B.E., C.B., D.S.O., E.D., Brigadiers Sir Kenneth Barron Fraser, C.B.E., E.D., and A. L. Dawkins, O.B.E., E.D., and Drs. William Bain, R. S. Steel, O.B.E., and B. C. Cohen. *As Associate Knight:* Dr. R. T. Paton. *As Dame:* Dr. Mary A. C. Ainscow. *As Commanders (Brothers):* Lieutenant-Colonels E. J. Selby, O.B.E., and G. Gregg, O.B.E., Major B. Moore, Air Commodore J. Magner, and Drs. E. L. Butler, W. L. Stewart, K. MacK. Macdonald, R. Rutherford, T.D., W. R. Cambridge, S. G. Nelson, and F. L. Firkin. *As Officers (Brothers):* Surgeon Commander H. M. Darlow, Wing Commander H. W. Whittingham, Mr. J. Ll. Temple, and Drs. A. J. Amor, C.B.E., J. W. McK. Nicholl, D. I. Acres, K. G. Bergin, W. H. Dunn, S. S. Datta, A. Burns, O.B.E., M.C., D. K. Gaitskell, S. Caruana, H. G. Vyse, O.B.E., J. S. McLintock, M. A. Byer, O.B.E., C. D. Bateman, H. G. Prest, L. D. Hodby, and A. N. Jacobs. *As Associate Officers (Brothers):* Drs. Haji Mohamed bin Mohd Ibrahim, F. Gerbode, and D. Harrington. *As Officers (Sisters):* Drs. Elizabeth M. Anderson and Mary E. Rolston. *As Associate Officer (Sister):* Dr. Marianne Neuman. *As Serving Brothers:* Drs. W. M. M. Douglass, J. P. Naudi, Essel Tan, William Oh, A. S. Browne, A. C. Mackay, C. G. Lees, R. D. Bridger, R. West, G. A. Neil, Chan Hee Chee, N. H. A. Mackinnon, J. W. S. Kasirye, W. M. Daly, J. S. Moffat, F. H. Hollingshead, O.B.E., T.D., G. W. Spark, J. C. Forbes, D. O. Hughes, A. R. Harbinson, I. Fletcher, P. A. Rodger, J. A. Moyse, H. Mandiwall, W. P. Blackstock, G. M. Gibson, A. L. Brown, C. P. F. Boulden, J. B. Hurll, M.B.E., W. A. Conolly, F. P. Opitz, L. W. Wing, and R. Marshall. *As Associate Serving Brothers:* Drs. M. Ahmad and J. N. Lewis. *As Serving Sister:* Dr. Margaret S. B. Langton.

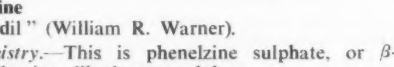
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Phenelzine

"Nardil" (William R. Warner).

Chemistry.—This is phenelzine sulphate, or β-phenylethylhydrazine dihydrogen sulphate:



Pharmacology.—Phenelzine belongs to a group of substances which inhibit the activity of the enzyme monoamine oxidase, thus preventing the destruction of serotonin, adrenaline, and noradrenaline.[1] Serotonin (5-hydroxytryptamine) is stored in many parts of the body in an inactive form. When released it becomes pharmacologically live and is rapidly destroyed when its immediate physiological function is complete. Monoamine oxidase plays a major part in the inactivation of serotonin by converting it to 5-hydroxyindole acetic acid. The inhibition of monoamine oxidase, therefore, causes the accumulation and continued activity of serotonin. High concentrations of serotonin are present in various parts of the brain, and these are parallel to the concentrations of monoamine oxidase. The function of serotonin in the brain is not known, but it is possible that it is a neurohumoral transmitter. Artificially high levels of serotonin in animals produce excitement and tremor.

The observation that iproniazid (also a monoamine oxidase inhibitor) had a euphoriant effect in the treatment of tuberculosis led to its beneficial use in cases of depression, and to the supposition that its antidepressive property might be due to the inhibition of monoamine oxidase and consequent increase in released serotonin. This theory is supported by the fact that reserpine, which causes the release, and thus the destruction and depletion of serotonin, occasionally causes depression. The simple equation of antidepressive action with monoamine oxidase inhibition is inconsistent with other known facts, however. No correlation has been found between the therapeutic effect of different monoamine oxidase inhibitors and the level of monoamine oxidase inhibition in the jugular vein. Some potent monoamine oxidases are not antidepressive and some resemble "tranquillizers" in their effect. Isoniazid, on the other hand, is not a monoamine oxidase inhibitor but has been used successfully in the treatment of depression.

Therapy.—Phenelzine is being tried in the treatment of uncomplicated primary depressive illness. There is as yet no adequate comparison between phenelzine and E.C.T., at present the most widely used treatment for depression, but it seems unlikely that the drug is as effective as E.C.T. When given to chronic schizophrenics who show depression, apathy, and inactivity, the drug has improved these symptoms, but other aspects of the disorder are unaffected and a considerable proportion of such patients become overactive and violent. The most common dosage is 50–100 mg. per day orally in divided doses, but up to 200 mg. daily has been given.

Contraindications.—Organic disease of the nervous system, liver disease, and blood disease. Phenelzine should be given with caution to elderly patients until further trial adds to our knowledge of its effect.

Toxicity.—Phenelzine seems suitable for ambulant patients because of its mild side-effects. The most frequent are drowsiness, dizziness, nausea, headache, and postural hypotension. All disappear on reduced dose. Purpura has been reported as a complication.

N.H.S. Basic Price.—100 tabs., 29s. 3d.

REFERENCE

1 *Brit. med. J.*, 1959, **2**, 1238.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Ammonia in the Gut

SIR,—We have been specially interested in the annotation concerning "Ammonia in the Gut" (*Journal*, January 9, p. 118), a paper of ours on gastric urease having appeared in the November issue of *Gastroenterology*.[1] It was there shown that gastric urease was present intracellularly, in the surface mucosal cells, and that it could not have originated from bacteria. There would be nothing like enough organisms present to account for the concentration of urease found. We referred also to the work of Cardin,[2] who noted the presence of urease in the human foetal stomach, and such urease could not have arisen from bacteria. Recently, in this laboratory, the existence of gastric urease was likewise demonstrated in the foetal stomach of the sheep.

The mucosal cells of the stomach are free of bacteria and no reasonable theory is at hand to explain how bacterial urease could be actively transported into the mucosal cells, even apart from the fact that urease would be easily destroyed by the action of the high acidity of the gastric juice. Further, the recent work on the effect of antibiotics, to which you refer in your annotation, indicates that the experiments supporting a bacterial origin of gastric urease were based upon the incorrect assumption that the pharmacological action of an antibiotic is limited to its antibacterial action.

In the present context it may be remarked that one of us (O. F.) has continued over years to use urea in large doses therapeutically for cases of duodenal and anastomotic ulcers, especially those resistant to standard measures; also pre-operatively to promote healing and lessen local reaction in the region of an ulcer. The results have been striking, and, though not 100% successful, can often add something of therapeutic value. It is not easy to prepare in an elegant way the concentrated urea solutions used, and this makes the treatment less attractive than many more ordinarily used. However, the patient, whose dyspepsia is controlled by urea, will persist despite the taste of the drug and other minor side-effects.

One of us (K. McG.) is obliged to the Medical Research Council of Ireland for a personal grant for the above work.

—We are, etc.,

EDWARD J. CONWAY. K. MCGEANEY.
OLIVER FITZGERALD. FRANCIS J. GEOGHEGAN.
Department of Biochemistry and Pharmacology, University College, Dublin; and St. Vincent's Hospital, Dublin.

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1 Conway, E. J., FitzGerald, O., McGeaney, K., and Geoghegan, F., *Gastroenterology*, 1959, **37**, 449.
2 Cardin, A., *Arch. Sci. biol. (Bologna)*, 1933, **19**, 76.

Poliomyelitis and Weather

SIR,—Your interesting annotation, "Poliomyelitis and Weather" (*Journal*, January 2, p. 47), draws attention to the remarkably low incidence of poliomyelitis during the hot, dry summer of 1959. Both poliomyelitis-like illnesses and the usual seasonal increase in enterovirus infections were nevertheless observed.[1 2] More than 500 stool specimens were

examined in this laboratory during the year. Most of the stools from which enteroviruses were isolated were received during the period June–September. The unusual feature was the apparent disappearance of poliomyelitis virus, of which only one strain (Type 1) was isolated during the year. Our specimens were collected from cases of aseptic meningitis, diarrhoea, and various other diseases in the Western and Eastern Regions of Scotland. Our experience was shared by other Scottish centres. Thus, during 1959, poliovirus was not isolated in Aberdeen; one strain was isolated in Edinburgh and one in Inverness, both of Type 1, and both in the first quarter of the year. (For this information I am indebted to Professor A. Macdonald, Dr. R. H. A. Swain, and Dr. H. Williams.) There is thus good evidence that poliovirus was virtually absent from the population of Scotland in 1959. The low incidence of clinical poliomyelitis must be attributed to this, not to immunization with Salk-type vaccine. However effective in preventing paralytic complications of infection, killed-virus vaccine could hardly be responsible for eradicating poliovirus from the community.

The prevalent enteroviruses in 1959 in this area were Coxsackie viruses, mainly of group A and type B5. These are being studied in detail because of association of some strains with paralytic disease in persons immunized against poliomyelitis. It remains open to speculation whether the shift in dominance from Type 1 poliovirus in 1958 to Coxsackie viruses in 1959 was due to immunological, virus-interference, or other causes, and whether the unusual weather had any relevance to the phenomenon.—I am, etc.,

N. R. GRIST.

Virus Laboratory,
University Departments of Bacteriology and Infectious Diseases,
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2 Duncan, I. B. R., and Sommerville, R. G., *Hlth Bull. (Edinb.)*, in press.

Chlorpromazine in Tetanus

SIR,—While welcoming the report of Drs. Ajai Shanker and L. S. Mehrotra of a randomized trial of chlorpromazine and paraldehyde in the treatment of 30 cases of tetanus (*Journal*, November 28, p. 1150), we should like to comment on several points which conflict with our own experience. Since 1956 we have treated nearly 500 cases of this disease in a special unit, the majority being in randomized clinical trials of chlorpromazine, barbiturates, and more recently tracheotomy and intermittent positive-pressure respiration.

We are surprised that Drs. Shanker and Mehrotra give a period of onset in Table I for each of their 6 patients with mild tetanus, since they have said that in such cases "rigidity (is) present without any spasm." We know of no other definition of the period of onset than that of Cole as "the time between the first symptom of the disease and that of the first reflex spasms."[1]

We have stated that chlorpromazine is usually effective in controlling the spasms of non-neonatal tetanus in a dosage of 100–150 mg. intramuscularly four- to six-hourly.[2] Smaller doses of 50 mg. four-hourly were often only effective if phenobarbitone sodium was also used, and we prefer this combination.[3,4] Drs. Shanker and Mehrotra criticize our high dosage of chlorpromazine which they claim to be "unnecessary and hazardous," yet they have used paraldehyde (a potent drug in the treatment of tetanus) in addition to chlorpromazine in their chlorpromazine group and can hardly be in a position to judge dosage of chlorpromazine when used alone. In our hands, however, chlorpromazine alone or in combination with a barbiturate is not invariably successful in controlling the spasms of severe tetanus, nor is the even more potent phenothiazine derivative, acetylpromazine.[5] The high dosage we sometimes find necessary is illustrated by the case of an African male aged 34 years who had an incubation period of 6 days and a period of onset of 20 hours. Treatment with chlorpromazine 50 mg. four-hourly and phenobarbitone sodium 180 mg. was started 18 hours after the first symptom—that is, during the period of onset. A total of 450 mg. of chlorpromazine with added phenobarbitone sodium 720 mg. was given intramuscularly during the next 32 hours. Despite this, spasms continued and a severe bout of laryngeal and generalized spasms with total apnoea could only be controlled by giving chlorpromazine 100 mg. intravenously. These recurred half an hour later, and amylobarbitone sodium 0.5 g. had to be given intravenously to prevent asphyxia. It was obvious that spasms could not be controlled using conservative measures. The patient was therefore curarized, a tracheotomy performed, and artificial respiration given by means of a Smith-Clarke respirator.

In neonatal tetanus chlorpromazine or acetylpromazine alone failed to control spasms in 75% of patients,[6] and it is our feeling that these drugs are useful in the treatment of this most severe form of the disease only when combined with a barbiturate.

We believe that the claim of Drs. Shanker and Mehrotra of a cure rate of 93.8% of non-neonatal cases in the chlorpromazine group that survived more than 24 hours in hospital gives a false sense of the effectiveness of this drug in the treatment of tetanus. The mortality rate in 27 non-neonatal cases using a combination of chlorpromazine and barbiturate, our best conservative method of treatment, was 33%, and 50% in severe cases,[4] mortality rates which we have since confirmed in a further series of 65 cases. We have recently started a controlled clinical trial to compare the value of neuromuscular block and intermittent positive-pressure respiration with the combination of chlorpromazine or acetylpromazine and barbiturate in the treatment of severe cases of tetanus. Although the number of non-neonatal cases is still too small for analysis, our preliminary results in 11 infants treated by total curarization and intermittent positive-pressure respiration indicate a definite reduction in mortality.—We are, etc.,

R. WRIGHT.
E. B. ADAMS.

Department of Medicine,
University of Natal.

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4 —— Wright, R., Berman, E., and Laurence, D. R., *Lancet*, 1959, **1**, 755.
5 Wright, R., *Trans. roy. Soc. trop. Med. Hyg.*, in press.
6 —— *S. Afr. med. J.*, in press.

Pitfalls in Chemotherapy of Tuberculosis

SIR,—I read the article on "Chemotherapeutic Pitfalls in the Treatment of Tuberculosis" by Drs. Graham Poole and Peter Stradling (*Journal*, January 16, p. 161) with attention, being especially interested in the patient who does not take his P.A.S. (para-aminosalicylate). I feel that frequently we do not spend enough time and care in seeing that the patient, at the onset of his treatment, understands its complexities. It is not unusual to find patients discharged from sanatoria or attending chest clinics with very little understanding of the importance of their "pills," etc. The initial diagnosis

of tuberculosis even nowadays is understandably upsetting to most patients, and they need help to grasp and accept the necessity of 18 months' treatment. Which of us, with our much greater knowledge, can be sure we, too, should not falter ?

I believe a great deal depends on the relationship established between doctor and patient in this disease. Unfortunately it is rare in this country for a patient with tuberculosis to remain under the personal care of one doctor even throughout his period of chemotherapy. More often he is diagnosed by one, transferred for initial treatment in hospital under another, and then referred to the appropriate chest clinic. I believe therefore that a very big responsibility, possibly for the whole course of the patient's disease, rests with the doctor who actually initiates treatment, usually in hospital. I think a difficulty arises here because a houseman may not have enough experience of the disease to realize his responsibility, and the consultant has not the time or opportunity for the necessary private interviews. It is no good explaining once—many patients are agitated simply by an interview with a doctor and remember nothing that is said ; it must be repeated until one is sure it is understood. The chest physician at the clinic has then something to reinforce when he first sees the patient.

I am convinced it is possible with some patients to create a relationship in which they feel free to say if they cannot take their P.A.S. With others this is not so, but many will admit defaulting if questioned rightly, and the position as regards further treatment can then be discussed with them. With others one fails completely. Many of these seem unable to accept that they have the disease at all, or need treatment, and in these cases I believe prolonged daily streptomycin injections would also be very difficult to maintain.

In conclusion, I believe that with greater initial care the number of defaulters could be lessened, and that we should not abandon the use of oral P.A.S. in those cases where by constant vigilance and encouragement we feel we may trust the patient.—I am, etc.,

London, W.11. J. M. WARD.

Blood Groups in Rheumatic Carditis

SIR,—The article by Drs. C. A. Clarke, R. B. McConnell, and P. M. Sheppard from Liverpool (*Journal*, January 2, p. 21) interested me greatly, as I have recently carried out in Glasgow a similar survey[1] confined to the ABO blood-group distribution.

It has already been shown[2] that susceptibility to rheumatic heart disease is inherited as a simple Mendelian recessive character. Applying this information to ABO blood-group studies would lead to an expected preponderance of group O among these patients, which is not shown in any of the published series. In Table IV of Glynn *et al.*[3] group O is depleted to augment groups B and AB, in the latter instance to an apparently significant level. Dr. L. E. Glynn, in a personal communication, considered this explicable on the basis of technical difficulties with AB grouping. In the Liverpool series the gain at the expense of O is in group A and particularly in group B, while in the 538 Glasgow patients the distribution is closely similar to the 5,898 controls. It is possible that these differences might be due to unavoidable selection in the control groups. The controls in the Taplow series[3] were entirely, and in the Liverpool series mainly, hospital patients (though excluding peptic-ulcer patients in the latter), while the Glasgow controls were blood donors. Dr. Clarke and his colleagues make this point in their discussion, and one might therefore be forgiven for the suggestion that the true answer might be found by the method they themselves used in investigating peptic ulcer,[4] using unaffected siblings as controls. It would also help to have the relation between hospital patients and the general population in respect of ABO groups defined.

In spite of these speculations it seems reasonable to conclude that if ABO inheritance has any real importance in rheumatic heart disease it would be evident already in the published data.—I am, etc.,

Southern General Hospital, Glasgow, S.W.1. GEORGE J. ADDIS.

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4 Clarke, C. A., Price Evans, D. A., McConnell, R. B., and Sheppard, P. M., *Brit. med. J.*, 1959, **1**, 603.

Thyroid Disease

SIR,—With reference to your leading article "Diagnosis of Myxoedema" (*Journal*, January 9, p. 115) I would like to submit that epiphora definitely is an important feature of myxoedema—i.e., hypothyroidism. In certain cases we have noticed some improvement of epiphora by treatment with thyroxine. —I am, etc.,

Sunderland Eye Infirmary, Sunderland. D. K. RAY.

SIR,—In his Lumleian lectures (*Journal*, January 2, p. 1, and January 9, p. 78), Professor E. J. Wayne does not mention the value of the abnormal ankle-jerk in the diagnosis of hypothyroidism. This sign, a characteristic delay in relaxation, was described by Woltman in 1918.[1] I saw this sign demonstrated in Dr. E. B. Astwood's Department in Boston in 1954, and have since found that it is by far the most reliable single sign of hypothyroidism, from my own experience.—I am, etc.,

Forest Group Radioisotope Unit, Connaught Hospital, London, E.17. A. A. G. LEWIS.

REFERENCE

1 See *Practitioner*, 1958, **180**, 634.

Plasma Pepsinogen

SIR,—I read with interest the paper on the value of plasma pepsinogen estimation by Miss Kathleen Edwards, Professor R. P. Jepson, and Mr. K. F. Wood (*Journal*, January 2, p. 30). In a letter to the *Lancet* (1959, **1**, 1207) I remarked on the close resemblance in the histological findings in the gastroduodenal mucosa in ulcer cases and those found in the thyroid in Hashimoto's disease. Sections of the gastroduodenal mucosa taken some distance from the ulcer have revealed that the increased lymphocytic aggregations in the mucosa often contain a material similar in staining properties to the cell content of the gastric glands in the vicinity, and it is possible that this material is in fact pepsinogen. Although it might well be argued that the histological findings are merely those of chronic inflammation, the profusion of plasma cells and the association of these latter with autoimmune processes does seem to suggest that chronic peptic ulcer may be an autoimmune disease.

In the same issue of the *Journal* you give an interesting annotation on autoantibodies in ulcerative colitis (p. 47) and mention the method described by Broberger and Perlmann[1] of obtaining antigen from the

colon. It has occurred to me that, if the same method could be applied to the stomach, then an antigen might be obtained which could be used for detecting circulating antibodies in peptic-ulcer cases. Future research may show that a common denominator for at least three diseases of the alimentary tract where the cause is as yet unknown—namely, peptic ulcer, Crohn's disease, and ulcerative colitis—may well be a defection of the autoimmune process.—I am, etc.,

Memorial Hospital, Peterborough. D. W. BRACEY.

REFERENCE

1 Broberger, O., and Perlmann, P., *J. exp. Med.*, 1959, **110**, 657.

New Epidemic of Gonorrhoea

SIR—In Jamaica urethritis (gonococcal and non-specific) is endemic and many G.P.s will see and treat some hundreds of cases yearly, mostly fresh infections, but sometimes infections which have been present up to several months. The causes of this situation are the general promiscuity and the large reservoir of asymptomatic chronically infected women. Our experiences may be helpful in England's "New Epidemic of Gonorrhoea" (*Journal*, October 10, p. 685), to which Jamaican-bred gonococci are apparently contributing.

All the emphasis in the letters in the *Journal* has been on the drugs used in treatment, but this is only half the battle. It is absolutely vital to explain to the patient the importance of "No squeezing, no liquor, and no girls for at least two or three weeks," and the great importance of never resuming intercourse with the original girl until she has been fully treated. This may all seem self-evident, but even in the best clinics these points are not always drilled into the man so that they are perfectly understood. I always make him repeat the points to me until they are perfectly clear. Sexual and manual traumata to the urethra will perpetuate any infection and make even penicillin useless. Finally, I always encourage the drinking of large quantities of water, as this has both a physical and psychological effect in washing away pus and sins. The drugs found most useful are these: initial treatment consists of a single injection of a one-dose vial of "triplopen" (benethamine penicillin 500,000 units, procaine penicillin 250,000 units, and benzylpenicillin 500,000 units), with oral sulphadimidine or "lederkyn" (sulphamethoxypyridazine) for three days. Those few cases which do not clear completely in a week will almost certainly do so on either "kemicitin" (chloramphenicol), 250 mg. six-hourly for 48 hours, or "mysteclin-V" (tetracycline-nystatin), 500 mg. twice daily for two days. The latter is much more expensive, but slightly more effective, and either drug may be combined with a single prostatic massage at the beginning of treatment.

There is little need for culturing except in the rarest cases, but there is every need for that little talk, especially in those types of patients who are most likely to be needing treatment.—I am, etc.,

Mandeville, Jamaica. L. D. LORD.

Cardiac Arrest

SIR,—Dr. R. S. Walton (*Journal*, January 16, p. 155) is to be warmly congratulated on the successful outcome of his cardiac massage for cardiac arrest following coronary thrombosis. However, his comment that with fibrillation "one may have time to wait and try the effects of electrical or chemical defibrillation" is misleading and requires correction. When the ventricles are fibrillating the circulation is at a standstill, and, if irreparable brain damage is to be avoided, the heart *must* be massaged and the lungs inflated. Intravenous drugs cannot of course reach the heart, and electrical defibrillation—which can only be done properly with the chest open—should be preceded always by massage. It is pointless to try to differentiate between cardiac arrest and fibrillation, since the circulation is arrested in both instances: there will certainly not be bleeding with fibrillation.

From Dr. Walton's statement that localized movements could be felt in the ventricles in his patient it seems likely that ventricular tachycardia, not fibrillation, was present. This arrhythmia is known to respond to procaine.—I am, etc.,

London, W.5. A. HOLLMAN.

SIR,—One reads, usually in the lay press, of some fortunate person, whose heart having stopped, has it manually massaged (following a heroic operation for reaching it, performed under great difficulties, and with little or no antiseptic precautions), in which after 15 minutes the heart started to work once more and the patient lived.

One was under the impression that 15 minutes of anoxaemia would almost certainly be too much for recovery of the brain and of the heart muscle. Apparently this is not always so—but how is it explained on modern physiological lines? Are we exaggerating the dangers of anoxaemia? The older ones of us must remember seeing patients undergoing anaesthesia and, in the early stages, getting into what was thought to be spasm, becoming very cyanosed indeed, duly recovering, and apparently none the worse subsequently. I can remember patients to whom this happened 30 years and more ago who are still very well and apparently very normal.—I am, etc.,

London, N.W.8. HENRY CHURCHILL.

Human Inoculation with Parainfluenza Viruses

SIR,—You recently published an article by my colleagues and myself (*Journal*, November 7, p. 909) describing the inoculation of 38 human volunteers with strains of parainfluenza viruses Types 1 and 3. Two volunteers received a strain K, which we said belonged to parainfluenza Type 3. Dr. R. M. Chanock has studied this virus and informed us recently (personal communication to Dr. M. S. Pereira) that the virus is in fact a strain of Type 1. We have now confirmed this. The error in the publication is much regretted, and we hope that this letter will be noted by all those interested by our paper. The error arose because the virus was not fully tested with Type-1 serum owing to a misunderstanding between two laboratories. We wish to point out, however, that the identity of the other two strains (Cop 222 and Moss) was fully established, and our general conclusions do not, in our view, require modification.—I am, etc.,

Medical Research Council Common Cold Research Unit, Salisbury, Wilts. D. A. J. TYRRELL.

Primary Varicella Pneumonia

SIR,—The interesting and detailed report of a case of primary varicella pneumonia by Surgeon Lieutenant O. McCarthy (*Journal*, November 28, p. 1155) did not, perhaps, do full justice to the frequency of this condition. Previous reports of chicken-pox involvement of the lungs occurring in Great Britain are due to Boucher[1]

and to McLachlan,[2] but these were only short notes. As with the other "rare" complications of the exanthemata, primary varicella pneumonia is often found when it is actively looked for.—I am, etc.,

Brooklyn, 5. New York. HARRY WIENER.

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[1] Boucher, P. R., *Lancet*, 1953, **1**, 854.
[2] McLachlan, I. M., ibid., 1953, **1**, 1152.

Imipramine in Depression

SIR,—The problem raised by Dr. Felix Post (*Journal*, December 5, p. 1252) in regard to the optimum period of administration of imipramine is an important one that has not as yet been answered satisfactorily. One has the impression that the larger proportion of patients who respond to imipramine do not relapse when the drug is discontinued after a period of about six months. Nevertheless some do. It could be that some "spontaneous" change has occurred in the former group—a similar suggestion was once made about the effects of electroconvulsive therapy (E.C.T.)—but it would be difficult to establish this point. I suppose it could be shown by continuing to treat the trial group with placebo indefinitely, but this is not a procedure I would care to justify.

Dr. Post's second point concerning the desirability of giving tablets or E.C.T. is one on which it would seem reasonable to consult the patient. I find that most people would rather have tablets. It is true that confusion may occur during the administration of imipramine, but it is uncommon and did not occur in any of the cases reported in the trial. We have seen it very occasionally in elderly patients and in one middle-aged man.

I am afraid Dr. E. K. Ledermann (*Journal*, December 12, p. 1331) has failed to appreciate certain points made in our paper. We are quite aware that 250 mg. of imipramine daily is often an unnecessarily large dose. We gave this amount in an attempt to obviate the possibility that failure in some cases might be due to inadequate dosage. With regard to his second suggestion that psychotherapy should have been given in addition to imipramine, one is reminded of the attitude of some therapists—particularly in North America—who grudgingly administer E.C.T. to severe depressives, but only as an aid to psychotherapy. The trial was of imipramine, not of the combination of imipramine and psychotherapy. Whether the latter is effective or ineffective is not in question, though to say that "successful psychotherapy makes it possible for the drug to act" is at best mere speculation. If, as Dr. Ledermann concludes, the trial has shown that imipramine is an effective drug in depression it has achieved all we set out to do. The question of "how effective it can be" raises problems of a quantitative nature for which no satisfactory solution is in sight.

Dr. G. Bram (*Journal*, December 26, p. 1485) reports that he has found that cases of agitated depression prove to be intolerant of imipramine. This has been infrequent in our experience. On the other hand, it has been apparent that patients with neurotic disorders, including depression, are particularly sensitive to the side-effects of the drug. I wonder if this discrepancy can be accounted for in terms of semantic differences? I cannot agree that the "more serious depressions" do not respond to imipramine. I accept that some show little or no response, but many undoubtedly do.—I am, etc.,

Department of Psychological Medicine, Royal Victoria Infirmary and King's College Medical School, Newcastle upon Tyne, 1. L. G. KILOH.

SIR,—As "tofranil" (imipramine hydrochloride), one of the new anti-depression agents, is now widely used, it is important that its significant side-effects be generally known, albeit that some occur uncommonly. Particularly is this so now that the drug is prescribed for psychiatric out-patients and in general practice, where the patient is seen less frequently than when in hospital.

The common side-effects of dryness of the mouth, tachycardia, sweating, constipation, disturbances of accommodation, the effects of hypotension, together with the less frequently occurring paraesthesiae, allergic reactions, and photosensitization, are fairly well known. To these must be added psychiatric relapse and skin reactions when the drug is discontinued abruptly, mild Parkinsonism, and the more recently described incoordination of motor activity as evidenced by falling, dysarthria, and coarse tremor. Finally, we have in our own practice recently noted the development of jaundice and also hypomania in patients receiving therapeutic doses of imipramine.

Three female cases of involutional depression developed obvious jaundice while on no other possibly contributing drug therapy than imipramine. Repeated liver-function tests revealed changes very similar to those occurring in chlorpromazine jaundice. These cases were separated temporarily by several weeks, there were no contacts with cases of infective hepatitis, none of them had any history of gall-bladder trouble, and all cleared in under a fortnight on immediate cessation of imipramine administration.

We have had three cases of hypomania which are interesting in that the development of the hyperactive state was not associated with the giving of electroconvulsive therapy (E.C.T.), but two of the cases were constitutionally of a manic-depressive temperament and their swing from a depressive to a hypomanic state was akin to that not infrequently occurring when E.C.T. is given. This personality type may be particularly susceptible to hypomanic reaction with imipramine. Further, it transpired that two of these patients had, unbeknown to us at the time, received previous imipramine therapy, during which they developed signs of hypomania which had subsided when the imipramine was discontinued. These recurrences, as also one patient suffering from hypomania for the first time (while on imipramine), proved more intractable, and did not subside in a fortnight, as in a series recently described.[1] This one case continued in hypomania for several months before subsiding, and in a present case continued in-patient stay has been necessitated on account of the condition.

This communication is intended to stress the fact that although some of the side-effects are merely inconvenient when compared with the underlying condition for which the drug had been given, and would require only a reduction of dosage, others may have drastic physical and mental results. The possibility that effective E.C.T. may be delayed and that there may be increased hazards from suicide must also be considered. These findings are particularly significant when using a drug which, in contrast to the wide claims made for it, appears to have a more limited sphere of action, and where success is unpredictable, even in those particular groups—that is, endogenous and involutional depressive states with retardation—where it has been found most likely to be of value.

More recently, two cases have come to our notice in which patients, who were receiving monoamine oxide inhibitors (*Journal*, December 5, p. 1238) at the time, took large doses of chloral and aspirin respectively. Amongst the symptoms which followed were seen muscular twitching and epileptic fits. This raises the question of serious effects occurring as a result of synergic action with normal doses of these drugs if a

large dose of another preparation is given. It may be possible shortly to report these cases more fully. We would be interested to know if effects of this nature have been noted by any other practitioners.—We are, etc.,

Cheadle Royal, Cheadle, Cheshire. M. SEGAL. E. HOWARTH.

REFERENCE

[1] Leyberg, J. P., and Denmark, J. C., *J. nat. Sci.*, 1959, **105**, 1123.

SIR,—Dr. E. K. Ledermann's letter (*Journal*, December 12, p. 1331), referring to the use of imipramine ("tofranil"), makes a very good point. There is a large area of neurotic, and perhaps also of psychotic, illness which is hardly touched by chemical or physical therapies. The most these can do is to make well what was ill. This leaves the patient as much subject to his stresses as before and likely to react to them in the same way: if he broke down under them then, in what way will he be less vulnerable now, unless his conflicts are dealt with and his instincts made familiar friends instead of ferocious enemies? He cannot achieve this alone, and when his intolerable symptoms are removed and he has become accessible, then psychotherapy may help him to manage his problems and stresses in a more satisfactory way, and so give him the chance of a permanent change for the better.

It is neither possible nor necessary to give deep or prolonged psychotherapy to every neurotic or psychotic patient. I am sure, however, that most patients can accept something in the way of psychotherapy. If the opportunity is missed, as so often it is, small wonder that such patients relapse. I too have used imipramine in a number of depressive cases, and especially for the agitated depressives of the menopausal and post-menopausal years, and have found it a most useful drug. But I have found it much more effective in cases where the removal of the acute symptoms was accompanied or followed by the facing and acceptance of problems and stresses that still had to be borne.—I am, etc.,

Stroud, Glos. MARION B. COLEMAN.

What Does the Brain Do?

SIR,—Aristotle placed the "sentient principle" not in the brain but in the heart, but for a long time it has been believed that, "since all mental function depends upon cerebral function, the brain is the organ of the mind,"[1] and that mental physiology "belongs" to the neurophysiologist. Sherrington,[2] however, towards the end of his brilliant researches on brain mechanisms, concluded, "We have to regard the relation of mind to brain as not merely unsolved, but devoid of a basis for its very beginning," and in my book[3] I discuss some of the evidence for supposing this basis to be in the muscular, vascular, and special sense tissues, and not in the central nervous system, which, however, is a necessary ancillary.

Hughlings Jackson placed highest level function in the frontal lobes, but as these lobes, or even the parietal, occipital, and temporal lobes, may be surgically removed "without great impairment of consciousness,"[4] it is becoming accepted that there is no locus for the mind in the cerebrum. Penfield[5] now believes that "centrencephalic organization provides the neural basis of consciousness," but this is not accepted in its entirety by Walshe,[6] who would limit this area at most to visceral consciousness alone. It therefore appears that the problem of mind to brain is no longer a neurophysiological one, and the study of the mind becomes again the responsibility of the general physiologist.

Lord Adrian, however (*Journal*, July 25, 1959, p. 78), pictures "a nervous machine which can make intelligent decisions" as a basis for further study, which I believe may confuse rather than clarify mind/body relationship, and which leads to deterioration of word meanings. The word "memory" is now generally applied to traces of energy systematically stored in electronic devices, and likewise "intelligent decisions" may lose much of its present psychic meaning. Although the central nervous system in some respects may be likened to the selector mechanisms of automatic telephones, such comparisons always distinguish between rather than elucidate nervous and mental functions. When physiologists re-assess "What does the brain do?" on the basis of the already existing sufficient knowledge, we shall find the way cleared for the much-needed research upon the relation of mental and emotional states to the muscular, vascular, and special sense tissues of the body.—I am, etc.,

Bournemouth. F. A. PICKWORTH.

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[1] Nielsen, J. M., and Thompson, G. N., *The Engrammes of Psychiatry*, 1947. Charles C. Thomas, Springfield, Ill.
[2] Sherrington, C., *The Brain and its Mechanisms*, 1933. Cambridge University Press.
[3] Pickworth, F. A., *New Outlook on Mental Disease*, 1952. Wright, Bristol.
[4] First International Congress of Neurological Sciences, Brussels, July, 1957. 2nd Journeé Commune. Bailey, P., p. 136.
[5] Ibid., Penfield, W., p. 13.
[6] Ibid., Walshe, F. M. R., p. 144.

Turner's Syndrome

SIR,—I suspect that Turner's syndrome is uncommon: it is not mentioned in either of my text-books of pathology (each printed within the past 10 years) even in small print. On this assumption, I am intrigued by the implication in the first paragraph of the article by Drs. A. W. Spence and C. W. H. Havard (*Journal*, December 12, p. 1288) that the incidence of disease in these cases requiring laparotomy is high. Were these "similar cases in which rudimentary ovaries had been found at laparotomy or at necropsy" also sufferers from coincident appendicitis, as was their own case? If so, the fact is surely worthy of comment.—I am, etc.,

Blackburn, Lancs L. M. ELLIS.

Mothers' Preference in Confinement

SIR,—We read with great interest the article by Drs. I. Gordon and T. F. Elias-Jones (*Journal*, January 2, p. 52), as a similar survey is now being conducted in Blackpool. The scope of the survey is limited to those mothers who have had at least one baby in hospital (or nursing-home) and one at home, and they were asked to complete a confidential questionary which was given to them by the health visitor at the first home visit and collected at the clinic or next home visit. The mothers were asked to express a preference for home or hospital confinement, if their confinement was expected to be normal. Furthermore, they were asked for reasons for any expressed preference and for criticisms and suggestions for improvement in the hospital, domiciliary, and clinic services.

An extract of the first 89 results since the survey was initiated in August, 1959, is shown below:

Number of mothers favouring home confinement	78 (87%)
Number of mothers favouring hospital confinement	11 (13%)

The 11 mothers who favoured hospital confinement had 26 babies in hospital and 16 at home, of which the last confinement was at home in 5 cases. Similarly, the 78 mothers favouring home confinement had 125 babies at home and 128 in hospital, of which the last confinement was at home in 55 cases.

Reasons for Home Preference in Case of 78 Mothers	
More natural and familiar surroundings and ability to relax	30
More privacy and better individual attention	17
Ability to look after the family	13
Less mental anxiety regarding welfare of the family	9
More freedom in the management of the baby, especially question of breast-feeding	5
Better relationship with medical attendants and midwives	4
Reasons for Hospital Preference in Case of 11 Mothers	
More rest and less work	6
Less worry	2
Every requirement at hand in an emergency	2

In Blackpool approximately 80% of births occur in hospital, but those who have experienced hospital and domiciliary care seem to prefer to have babies at home, provided there are no foreseeable complications and social conditions are satisfactory. Although the numbers are much smaller than the Ilford survey, the results are very similar.—We are, etc.,

D. W. WAUCHOB.
D. P. W. ROBERTS.

Municipal Health Centre,
Blackpool.

Hypnotic Suggestion in Domiciliary Midwifery

SIR,—At a meeting held on April 15, 1959, at the Royal Society of Medicine on the role of the general practitioner in the midwifery service,[1] the General Secretary of the Royal College of Midwives referred to difficulties arising as a result of the Cranbrook Committee's recommendations that the general-practitioner obstetrician should be present at the delivery whenever possible. She wonders whether he will be satisfied with the role of helping the mother with the gas-and-air or "trilene" machine while the midwife does the delivery.

I feel that domiciliary obstetrics would become a perfect example of team-work between the doctor, midwife, and the mother, if general-practitioner obstetricians would take the trouble to train their patients in hypnotic relaxation antenatally. Thus the midwife would carry out all normal deliveries, while mother and doctor co-operated in making the delivery an exciting, controlled, and pleasant affair for all concerned. Potentially dangerous anaesthetic machines could then be abandoned for most patients and the mother allowed to enjoy to the full one of the supreme moments of her life.

My impression is that a mother who has gone through a delivery using hypnotic suggestion gains permanently in self-confidence, presumably as a result of her having proved her ability to control her emotions and her body during childbirth. Domiciliary obstetrics is a "tailor-built" affair as opposed to the hospital's production-line technique. Although mass-production methods have improved enormously, there are still many who prefer their suits made for them.—I am, etc.,

J. W. F. LUMSDEN.

Department of Obstetrics and Gynaecology,
University of Malaya,
Singapore.

REFERENCE

1. *Proc. roy. Soc. Med.*, 1959, **52**, 711.

Family Planning Advertisement

SIR,—The spate of correspondence in the *B.M.J.* over the *Family Doctor* advertisement is nauseating and disgusting, and its latest development in dragging in religious controversy is unworthy of our profession. I am sure that our founder, Hastings, would have turned in his grave if he had known that our great Association had entered the realms of popular journalism. Even if money is being made, surely our dignity and decency must be considered.

There is an old proverb "Let the cobbler stick to his last." Obviously we should cease to sponsor commercial publications and confine ourselves to our proper sphere. Let us sell the publishing rights of *Family Doctor* to one of the many firms whose business it is to deal with suchlike. It is time our Council read the history of the B.M.A. and rediscovered the purposes for which we were founded.—I am, etc.,

Kingskerswell,
Devon.

JOHN V. MAINPRISE.

SIR,—It is not only Roman Catholics who view with concern advertisements for the Family Planning Association in a lay journal, as also the highly organized propaganda in favour of the products of a powerful industry.

The writings of the Family Planning Association make several assumptions which are not based on fact. (1) They assume that bringing a child into the world must be an act of expediency, rather than one of faith. The implication is that a child should not be born unless the parents are sure that they can give it a good home and a good education. As this situation, particularly during financial depressions and in wartime, does not hold, the population must inevitably fall. (2) It implies that it is quite normal for mothers to have children at intervals of three or more years. This is bad for the mother, as it has been shown that, if she has her babies at intervals of one or two years, this is healthier than to have them at intervals of three or more years. It is also bad for the children, for, instead of there being a real family "of steps and stairs," there is a group of psychologically "only" children.

There is no talk of four or five children, as an act of faith. There is no indication that, if in a given stock the parents always aim at two or three children, that stock will die out in a few generations. There is no mention of the solitary and pessimistic individual who belongs to a dying stock, nor of his optimistic counterpart—the man who belongs to a stock that is steadily increasing, in families of five or more.

It is not usually recognized that, under pre-war conditions, it was usual for the professional man of 65 here to have one or two unmarried children in the twenties, whereas in other countries he would have had several grandchildren by the age of 55. The difference between these two situations is that between a social group which is dying out and one which has a potentially vigorous future.

Some years ago I examined the families of 915 medical men in *Who's Who*. Their average age was 62.6. Of these, 438 were in the Forces or abroad; these married at

the average age of 34.4. The 477 who were resident in the U.K. married at 31.9, the mean average for both groups being 33.3. Those with titles (211) had an average of only 1.65 children each, the figure being the same for 43 medical F.R.S.s. The percentage of those with five or more surviving children was 4.7. Yet it has been found by demographers that, in a community whose population is stationary, a percentage of 18 would be expected to have five or more children. Since in any community less than 20% of the parents in the present generation produce over 50% of the next generation, it is of vital importance whether the 20% are inferior or superior to the average. If the parents of large families are inferior, the group will deteriorate ; if superior, it will improve. One would hope, therefore, that members of our profession who are mentally and physically above the average will give more than their share of children to the next generation, instead of fewer.

The reasons why, in the twentieth century, marriage as an institution for carrying on the race has failed in the professional classes have been late marriage, contraception, and, too often, imitation of the more affluent families, who, in fact, have succeeded in having families above survival level. Bearing in mind the above facts, I think the profession would be well advised to take further counsel before advocating wholesale adherence to a policy of having babies as a matter of expediency, rather than aiming at four or five children during the first ten years of marriage, as an act of faith. —I am, etc.,

London, W.1. A. SPENCER PATERSON.

SIR,—I am astonished at the action of the Committee in preventing the Family Planning Association's advertisement. Please add my name to those who think this is quite unconstitutional and undemocratic. I consider the advertisement *should* be published.—I am, etc.,

Bath. T. S.-B. KELLY.

SIR,—Other members of the B.M.A. besides Dr. R. Hamber (*Journal*, January 23, p. 280) will hope that *Family Doctor* will be read by a wide public and not offend a section. Recently, readers of reputable periodicals in which F.P.A. advertisements have begun to appear have written to complain, or have simply discontinued taking them. In one case no further advertisements were accepted and the complainant received a letter saying: "The people in our office did not like the advertisement either."

Conscientious objection to artificial contraception (which after all is the F.P.A.'s *pièce de résistance*, although it may have less controversial side-lines which are quoted as if in extenuation) is not limited to Catholics. It is not at all incompatible with the pronouncement of the Anglican bishops at Lambeth that the methods by which individuals limited their families should be such as their consciences allowed.—I am, etc.,

Durham. VALERIE ADAMSON.

*** This correspondence is now closed.—ED., *B.M.J.*

"Family Doctor" on Food

SIR,—Dr. Dick Glover (*Journal*, January 23, p. 281) commits the unpardonable sin of quoting out of context. He quoted Hutchison in *Food and the Principles of Dietetics* (p. 254): "The importance of sugar as a modern food commodity cannot be over-emphasized." The next sentence continues: " . . . that dietitians are beginning to ask whether there be not great danger in eating sugar in the quantities we do."—I am, etc.,

Research Department, Bovril, Ltd., London, E.C.1. A. E. BENDER.

Cross-infection in Hospital

SIR,—I was interested by Dr. W. E. Crosbie's letter about cross-infection in hospital (*Journal*, December 12, p. 1331) and agree that the improvement of hygiene standards depend on the enthusiasm of the staff. But in such matters the staff must have a leader and the obvious person to fill this role is the Control of Infection Officer.[1]

Very little has been heard of this official in the medical press, and small wonder ; he does not have an enviable task. Yet there is much basic work to do. This does not mean controlling outbreaks and checking that the control of infection register is up to date. True prevention means investigating familiar hospital routine in the ward, the theatre, the kitchens, and the offices. It is time-consuming and needs much discourse with medical, administrative, and architectural staff. It means laying down a policy of preventive discipline, from the wording of printed matter sent to patients about to enter hospital, to notification of infection by family doctors after the patient has been discharged. It also means checking that the policy is honoured by all.

Unfortunately there is little material reward in preventing disease and only an occasional whisper of thanks. The Chief Medical Officer to the Ministry of Health in his 1958 Report[2] recognizes this when he writes: "To detect, to treat, and to cure any established disease rightly merits the gratitude and appreciation of the individual so restored to health, but to keep him free from such an experience, with all the disturbance of life it may mean, is surely equally meritorious." It is too bad we still have to convince each other that this is so and distressing to analyse why this should be.—I am, etc.,

Devizes, Wilts. K. J. ADAMS.

REFERENCES

[1] *Staphylococcal Disease in Hospital—Report of the Subcommittee*, Ministry of Health Central Health Services Council, Standing Advisory Committee, 1959. H.M.S.O.
[2] *Report of the Ministry of Health for the Year 1958, Part 2, on the State of the Public Health, Being the Annual Report of the Chief Medical Officer*, 1959. H.M.S.O.

Safety Harness for Car Occupants

SIR,—I should like to add a few words to the correspondence which has recently appeared in the *B.M.J.* on the subject of safety harnesses for motor vehicles. I fitted safety harness to my car just over 18 months ago after reading some appalling accounts of motoring injuries. There are others better qualified than I to stress the advantage of such harness from a safety point of view, but there are two other benefits worth considering.

Firstly, it should be stressed that when travelling alone with children the driver has no worry about heads banging the windscreen and doors being opened. Secondly, a safety harness constitutes a great advance in comfort for front-seat passengers. This is particularly noticeable of course on poor roads, but even when motoring on the smooth-surfaced roads of Britain a safety harness is a decided advantage to a front-seat

passenger. Such a harness releases the passenger from the consideration of road contour, and the many small movements of legs and arms normally required to maintain the passenger's body in contact with the seat on winding and twisting roads are completely obviated. At the end of a long car-journey a front-seat passenger who has been wearing a safety harness is very much less tired than one who has not been so equipped. I believe that if this great increase in passenger-comfort were more widely realized the use of safety harness would become much more widespread.—I am, etc.,

Salisbury, Southern Rhodesia. TOM D. BLEAKLEY.

Reading the Number Plate

SIR,—The vision test for drivers is, as Dr. S. Chaplin says (*Journal*, December 26, 1959, p. 1487), hopelessly variable and inaccurate. But it is not apparently generally realized that, while a candidate may need glasses to pass even this rough check, there is no law to require him to wear them when actually driving; the purpose of the test is therefore defeated. It would be very simple to mark the licence "with glasses" if they were needed to pass, and require the driver always to wear them when driving.—I am, etc.,

Canterbury. R. A. D. CRAWFORD.

POINTS FROM LETTERS

Family Planning Advertisement

Dr. EVA TREGILLUS (Darlington) writes: After reading your leading article "O Tempora!" (*Journal*, January 2, p. 42) in which you took some pains to assure your readers that there had been no attempt by a minority group to prevent, by threats, the publication of the Family Planning Association's advertisement, I was rather surprised to read Dr. A. Reeves's letter (*Journal*, January 16, p. 198). Dr. Reeves, who says he is a member of the Guild of St. Luke, SS. Cosmas and Damian, writes: "Can the Association afford to lose two or three thousand seven guineas?" From the context this apparent threat of withdrawal of membership would appear to be connected with the advertisement referred to above.

Ghana Medical Service

Mr. HARVEY JACKSON (The National Hospital, Queen Square, London, W.C.1) writes: I very much regret that in my recent letter to you (*Journal*, January 2, p. 60) I did not use the correct designation of the military hospital in Accra, which is the Ghana Military Hospital, as General Sir Alexander Drummond points out in his letter (*Journal*, January 16, p. 204). I should like to draw attention to the fact that the institution is a national one so far as the State of Ghana is concerned, and I hope that my misstatement has not led to any lack of appreciation of the true position.

Cardiac Arrest

Dr. S. K. ROGERS (Mount Isa, Queensland) writes: The difficulty is diagnosis in many cases. Time is short. It should not be wasted in trying to discover by auscultation or palpation if breathing has ceased or whether the heart is still beating. As soon as suspicion occurs a small incision can be made over the fourth left intercostal space (let us hope that dextrocardia is not present). If even a trace of arterial bleeding is seen the operator can wait, and, if all goes well on other treatment, no harm has been done and all that is required is a stitch. If there is no arterial bleeding the incision can be extended into the thorax, the whole procedure taking only seconds. Any other diagnostic steps waste time and may take up most or all of the generally accepted, precious four minutes.

Obituary

E. H. R. HARRIES, M.D., F.R.C.P., D.P.H.

Dr. E. H. R. Harries, formerly chief medical superintendent of the infectious hospitals service of the London County Council, died at University College Hospital on January 12. He was 78.

Eric Henry Rhys Harries was born on January 12, 1892, and studied medicine at the London Hospital, to which he won an entrance scholarship, and where he later gained several prizes. Graduating M.B., B.S. in 1907, he proceeded M.D. in 1909 and obtained the D.P.H. of Liverpool a year later. He took the M.R.C.P. in 1936 and was elected F.R.C.P. in 1942. After qualification he worked first as senior medical officer at the Victoria Hospital for Children, Tite Street, Chelsea. Later he went to Liverpool as senior resident medical officer at the City Hospital, Fazakerley. During the first world war he served in the R.A.M.C. and was attached to the base isolation hospital in Mesopotamia, later becoming C.O. of the Central Laboratory, Murree, in the Punjab. Having worked for a time as tuberculosis officer in Newport, Monmouthshire, he was appointed medical superintendent of the City Hospital, Little Bromwich, Birmingham. Over the course of years he became one of the leading experts on infectious diseases in Britain.

H. S. B. writes: Dr. E. H. R. Harries was one of the leaders in the field of common infectious diseases during the quarter-century 1920 to 1945, when this group of diseases constituted one of the most formidable of the threats to life and health of the young in this country—as indeed, it still does in many countries. After his early training in the Metropolitan Asylums Board fever hospitals in London he became medical superintendent of the City Hospital, Little Bromwich, Birmingham. There his main concern was with the large numbers of patients admitted with scarlet fever and diphtheria. At this period he must have been greatly impressed by the dangers of cross-infection in overcrowded children's wards, and he induced the Birmingham public-health authority to embark on a major scheme of extension of the Little Bromwich Hospital. He was also one of the pioneers in the study of diphtheria immunization in groups specially exposed to the infection—children in residential nurseries and the nursing staffs of hospitals for infectious diseases. In the decade 1920–30 he contributed articles on barrier nursing in wards, diphtheria immunization, and streptococcal antitoxin in scarlet fever.

In 1932, soon after the L.C.C. assumed control of the fever and public-authority general hospitals in London, he was appointed medical superintendent of the North-Eastern Hospital (now St. Ann's Hospital, Tottenham), which, at that time consisted in great part of hutted wards erected many decades previously to meet an emergency epidemic. Fresh from his experience of hospital construction in Birmingham, Harries was the first to benefit from the forward-looking policy of the L.C.C. in hospital rebuilding, and the North-Eastern Hospital was entirely reconstructed with modern isolation wards containing five 4-bedded and five 2-bedded units and also one single-bed unit, as well as with other wards composed completely of single-bedded isolation units. This was the most advanced design for fever hospitals in the 1930s. The expensive pavilion system of ward units was retained as still being necessary at that time (although in the modern conditions of the 'sixties it might well be superseded by the ward block system). Dr. Harries's Milroy lectures to the Royal College of Physicians in 1935 on control of infection in children's wards, based on his experience in crowded scarlet-fever, measles, diphtheria, and whooping-cough wards, attracted much attention, especially in paediatric circles, by revealing the extent and gravity of the cross-infection existing in children's wards, especially in winter, when they were generally allowed to become grossly overcrowded. He was a stalwart supporter of the Ministry

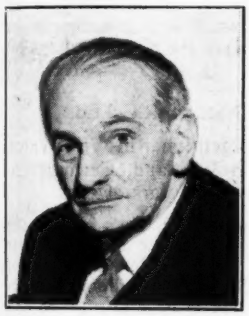
of Health's standard of bed spacing in fever hospitals (12 ft. between bed centres and 144 sq. ft. of floor space), which appeared to have been derived from the experience of the medical superintendents of the M.A.B. fever hospitals.

Dr. Harries was twice president of the fever hospitals group of the Society of Medical Officers of Health—a very active group at that time—and later was president of the Section of Epidemiology of the Royal Society of Medicine. In 1940, in co-operation with the late Maurice Mitman, he produced a textbook on clinical practice in infectious diseases which was well received and is now in its third edition. He retired from the service soon after the war and thereafter became somewhat of a recluse.

B. B. NOBLE, M.B., B.S.

Dr. B. B. Noble, who retired from practice in Choppington, Northumberland, in 1958, died at his home at Rothbury on January 11, at the age of 72.

Benjamin Bell Noble was born at South Shields on December 12, 1887, the son of John Noble, a pharmaceutical chemist, and was educated at South Shields High School. He studied medicine at the then Durham University College of Medicine, Newcastle upon Tyne, graduating M.B., B.S. in 1911. For the next two years he was assistant to the late Dr. Andrew Smith at Whickham, Co. Durham, in a busy country and colliery practice. As a result of his experience there he decided to spend his life working as a practitioner in a colliery area, but before doing this to gain experience in resident hospital apopintments. He therefore became resident medical officer at the Fleming Memorial Hospital for Sick Children, then house-physician and later house-surgeon in the Royal Victoria Infirmary, Newcastle. The outbreak of the first world war came near the termination of this last appointment, and in August, 1914, he volunteered for service in the R.A.M.C. Immediately accepted, he was sent to France in the early part of 1915 as a regimental medical officer and took part in the Battles of the Somme, being mentioned in dispatches and awarded the Croix-de-Guerre. After being wounded he returned to England and later served in India and Mesopotamia.



After demobilization he achieved his ambition by joining the late Dr. William Hudson in colliery practice in Choppington. Here he remained until his retirement, and, although the membership of the practice changed, he and his partners controlled and guided its destiny until it became the largest colliery practice in Northumberland. Great was his joy when in 1948 his son John Simpson Noble returned from military service and became an active partner. This joy was enhanced as he watched the increasing interest his son took in the affairs of the British Medical Association, culminating in his becoming a member of Council in 1957.

"Benjy" Noble, as he was affectionately called by his colleagues, was, as one would expect from a man who received his early training under Dr. Andrew Smith, a family doctor of the highest repute and integrity. The welfare of the patient was his only concern. He regularly came with them to Newcastle for consultations, and always tried to be present at their operations. How greatly this was appreciated by them was shown on his retirement: first his colliery patients suggested that a levy should be taken from their wages at the pit in order to make him a presentation, and then this was taken up by patients other than colliery workers, who made him another gift of appreciation.

Of an even temperament and studious nature, he took a very active part in associations and activities concerned with the welfare of his patients—the British Legion, of which he was local president, child welfare, the St. John Ambulance Brigade, and civil defence. He was a regular attender of medical meetings and postgraduate courses, and thus always kept abreast of progress in medicine. For a short time he held the post of medical officer of health of Bedlingtonshire. His standing in the profession was recognized by his election to the chairmanship of the Morpeth Division of the British Medical Association in 1927, and to the vice-presidency and, in 1954, the presidency of the Newcastle and Northern Counties Medical Society—the highest honour which can be given to a practitioner in the Northern Counties.

Reading was his hobby, and while his interests covered a very wide field they perhaps centred on philosophy and history, particularly that of Northumberland, for he loved the county and in his younger days had seen most of it on foot. He retired to Rothbury to spend two happy years in the hills he knew so well. Here he had a constant succession of visiting colleagues and friends, which delighted him. To mark the termination of his active medical life his son arranged a dinner to which those practitioners and consultants who had been associated with the practice over the years were invited. Each in turn paid tribute to Dr. Noble, whose masterly reply stirred the emotions of all present. Now he lies at rest in the heart of the Northumberland hills, as was his wish.

In 1921 he married Mary, the only daughter of Thomas Simpson of Hepscott. In his latter years Dr. Noble suffered from angina, and his wife watched and protected him with devoted care. To her and to his two sons and daughter we offer our heartfelt sympathy.—N. H.

Dr. ANDREW SMITH writes: B. B. Noble started his career as assistant to my grandfather, and I, in my turn, went out to Choppington as assistant to Dr. Noble. It was an inspiring apprenticeship. He had an eye and ear for the unusual, whether it be a rare amalgam of symptoms and signs or a bizarre quirk in a man's character, and he showed that the patient who had the disease was as interesting as the disease itself. He combined enormous enthusiasm for new ideas with scientific objectivity in assessing their worth, and never let himself be carried away by optimistic reports. He used to say in the pre-antibiotic days that only 12 drugs had any therapeutic value, and would count them off on his fingers, rejecting with irrefutable reasoning any brash suggestions for additions to the list.

When the College of General Practitioners started he joined immediately, and though he said he was too old to take active part his frequent presence at the early Faculty meetings had a consolidating effect. He was a great clinical-meeting man and the Newcastle medical societies were his spiritual home. He was at his best at the Sphalma, a small medical club whose members recounted their mistakes around a dinner table, and he seldom failed to enliven the evening with a masterly clinical description. He will be greatly missed.

Lady HUTTON, C.B.E., M.D.

Lady Hutton (née Emslie), emeritus consultant psychiatrist to the British Hospital for Functional Nervous Disorders, died at her home in London on January 12.

Isabel Emslie, the daughter of James Emslie, Deputy Keeper of the Privy Seal of Scotland, was educated at Edinburgh Ladies College and Edinburgh University, where she graduated M.B., Ch.B. in 1910, proceeding to the degree of M.D. (with honours in psychological medicine) two years later. Among the appointments she held after qualification were those of resident physician to the Royal Sick Children's Hospital, Edinburgh, and pathologist to the Stirling District Asylum. After further postgraduate study in Munich,

Vienna, and other European centres, she was appointed physician in charge of the women's wards at the Royal Mental Hospital, Morningside, Edinburgh, the first woman to hold this post. During the first world war she gave most distinguished service in the Balkans and elsewhere. Afterwards she returned to Edinburgh, but on her marriage she came to live in London and worked as a consultant psychiatrist. For some years she was a member of the Psycho-analysis Committee of the B.M.A. During most of the second world war she was in India, but after the war she continued to practise in London as a psychiatrist for a few further years until her retirement.

Dame LOUISE MCILROY writes: Lady Hutton was a very distinguished medical woman. In August, 1915, she joined the Scottish Women's Hospitals, and it was as a member of the Girton and Newnham Unit, of which I was *médecin-en-chef*, that I first became associated with her. She served with the unit in France and accompanied the unit when it was transferred to Serbia. After the war she was in charge of a unit which was attached to the Serbian Army, when it made its advance. She had to cope with typhus, malaria, and other epidemic diseases among the troops, and, in addition, performed surgical operations. She published a book in 1928 on her experiences entitled *With a Woman's Unit in Serbia, Salonika, and Sebastopol*. Among other books written by her were *Mental Disorders in Modern Life* (1940), *The Hygiene of Marriage* (9th edition, 1953), and *Woman's Change of Life* (1958). When the Serbian hospital closed she went to the Crimea in charge of Lady Muriel Paget's medical unit. Advised by the Royal Navy to leave for her own safety, she was transferred to Constantinople. It was there that she met her future husband, Major Thomas Hutton (later Lieutenant-General Sir Thomas Hutton), whom she married in 1921.

When Lady Hutton came to live in London she wished to take up mental work again, but found that as a married woman posts were closed to her. She then did a great deal of honorary consultant work and ran a clinic at the British Hospital for Functional Nervous Disorders. She served on many committees and always kept up her interest in Balkan countries, being chairman of the committee to raise funds for enabling Yugoslav women doctors to obtain postgraduate teaching in Britain.

Her long list of achievements has already been noted in the obituary notices, and I should like to pay my tribute to her as a member of my staff in the first world war. She was utterly efficient in her work, a "good mixer," and met with admiration from everyone with whom she came into contact. She was very versatile, and the concerts and entertainments which she organized made life for the troops in the East much more enjoyable than it would otherwise have been.

In the autumn of 1938 she joined her husband in India, and during the war she gave broadcasts on All-India Radio on music, poetry, and the arts in general; she was particularly knowledgeable about ballet. She was director of the Indian Red Cross Welfare Service until her return to England in 1946.

She received many decorations during her period of service, including the Serbian Order of the White Eagle, the order of St. Sava, the Royal Red Cross of Serbia, and the Croix de Guerre. She was a Commander of the Order of St. John of Jerusalem, and in 1948 she was appointed C.B.E.

D. A. K. CASSELLS, M.D., M.R.C.P.Ed.

Dr. D. A. K. Cassells, chief medical officer to the Alkali Division of Imperial Chemical Industries Ltd., died on December 16, 1959, at the Victoria Infirmary, Northwich, Cheshire, at the age of 63.

David Arthur Ketchen Cassells was born in Fifeshire on March 30, 1896, the son of a schoolmaster. Having served in the first world war as a combatant, he graduated M.B., Ch.B. at St. Andrew's University in 1923, and after holding a number of house appointments went into general practice at Leominster, Herefordshire. In 1938 he proceeded M.D., with honours, and left his practice for further study at the Postgraduate Medical School in London, taking the M.R.C.P. of Edinburgh in 1939. In 1940 he became medical officer to a factory, where, for the first time in this country, tetra-ethyl lead was manufactured. The process was full of little-known hazards, and in those pioneer days the continuous vigilance and devotion of Dr. Cassells were largely responsible for there not being a single case of intoxication in the factory. Such cases, however, did occur outside from time to time, and he was often called in to advise on these occasions. Together with Sir Charles Dodds he was author of the first objective account of tetra-ethyl lead intoxication to be published in this country. This paper, published in this journal in 1946, remains a classic.

During the second world war Dr. Cassells was appointed consulting physician to the Victoria Infirmary, Northwich, where he did memorable service, one of his activities being to assist in setting up a small panel of blood donors, which, until blood banks came into being, was of the greatest possible use. When the war ended he became first full-time chief medical officer to the Alkali Division of Imperial Chemical Industries, where he did so much to establish a very high standard of industrial medical service.

Always a gay companion, he was full of Celtic humour. His main preoccupations outside his work were bridge and fishing. He retired in March, 1958, but unfortunately his health had begun to break down before this, though he carried on with his job selflessly. He is survived by his widow.—A. H. B.

PHILLIP GIBBIN, B.Sc., F.R.C.S.Ed.

Dr. Phillip Gibbin, a general practitioner in West Wales, died suddenly at his home in Whitland, Carmarthenshire, on December 14. He was 58 years of age.

Phillip Gibbin was brought up on his father's farm in the village of Login, and was educated at the local grammar school in Whitland, and the Welsh National School of Medicine, Cardiff, graduating B.Sc. in 1924 and qualifying in 1926. After serving as an assistant in general practice and as a ship surgeon, his interest turned to surgery, and he took a number of hospital posts, including those of resident medical officer at the Park Hospital, Flixton, Lancashire, and senior house-surgeon at Rochdale Infirmary. In 1930 he became F.R.C.S. of Edinburgh. Then, although he seemed wholly elevated to surgery, he answered a call back to his native Carmarthenshire to help the late Dr. W. D. Owen with his country practice at Whitland, which embraced his native Login.

Phillip Gibbin became a very successful rural practitioner with an extensive practice, and his industry, together with his special interest in surgery, brought him far-reaching renown. In recent years, when his practice had become a three-man concern, he took on outside work as part-time regional medical officer for the Welsh Board of Health in the West Wales area. Unfortunately, he was involved in a serious motor accident a year ago, but he appeared to have made a good recovery and continued working to the end. He lived for two things—his work and his family—and from around these sources he also derived his pleasures. He was interested in everything and everyone around him, liking the simple things in life, especially if they had any rural or local connexion. Among his delights were his garden, greenhouse, and home wine-making, and his gifts to his friends from these sources were gladly received. He was an ardent reader and loved poetry. A Welsh-speaking Welshman, he was very interested in Welsh culture and history, being a keen member of the Honourable Society of Cymrodorion. He was a life member of the St. John Ambulance Brigade, delighting first-aid classes with his original approach to the subject and giving his last lecture a few days before he died.

Phillip Gibbin, believing that the only aristocracy was that of character and intellect, loved and understood the ways of

the people in his rural community. Old country characters delighted him, and he would repeat almost legendary tales of past and present local personalities. It pleased him to see people succeed, and equally did he vex over their reverses, lending a helping hand when he could. Many might have been surprised at his great acts of kindness, for he was inclined to hide a generous and gentle heart beneath a cloak of abruptness, which was itself possibly a cover for an inherent shyness and humility.

The deep sense of loss felt by so many was reflected by the attendance at his funeral of saddened people from a wide area, and the presence of so many of his colleagues showed the high regard in which he was held in his own profession. We mourn the loss of a good man and good doctor, and our sincere sympathy is extended to his widow and two young children.—G. K. P.

Dr. J. H. THOMAS writes from Port of Spain, Trinidad: Like others I was shocked to hear that Phillip Gibbin had died. He so dominated general practice in the contiguous areas of Pembrokeshire, Carmarthenshire, and Cardiganshire that it is difficult to visualize the district without him. His clinical judgment was always sound and his diagnostic acumen often brilliant. He was a big man with a striking personality and belonged to that *élite* fraternity which by common consent we affectionately refer to as "characters." Beneath a somewhat gruff exterior there dwelt a kind and sensitive nature which, strangely enough, he sought to hide. His retentive memory was appreciated not only by colleagues but also by those who heard him quote Macaulay, Gibbon, and Fisher in a resonant voice and with a characteristic fervour. There were many doctors in the district, but only one Phillip Gibbin. He will be missed for many years to come.

R. H. QUINE, L.R.C.P.Ed., D.P.H.

Dr. R. H. Quine died at Ballasalla, Isle of Man, on October 30 at the age of 100.

M. A. Q. writes: Richard Henry Quine was born in the mill-house of a deep valley in the Isle of Man, and from the beginning was always wanting to see what was over the crest of the hills or what was on the other side of any barrier. His schooldays at King William College were unmarked by any brilliance, probably because of this restless curiosity, but at Glasgow University, where he became a medical student, and later at Edinburgh University he came to life, won numerous prizes, and qualified in 1883 in a remarkably short time.

One of his first activities in an operating theatre was to spray the surgeon and assistants with a fine carbolic spray, so that their beards and frock-coats were dewed with moisture, and in one of the wards in the old Glasgow Infirmary, where he was a houseman, were iron rings fixed in the floors to which patients used to be fastened in the days when the ward was an operating room. He gave hundreds of anaesthetics using only chloroform dropped on to a folded towel, and never had a fatality by this method.

As a houseman in Edinburgh Infirmary he had in his charge the wards which Lister had used, and felt the influence of his mantle ever after. One old professor said to him, "Well, Quine, there may be such things as germs, but I am not superstitious." He was at a lecture given by Professor Gairdner when the professor received a telegram which he read to the class with great emotion: it was from Koch in Germany, saying he had isolated the bacillus of tuberculosis. After qualifying he made a few voyages as a ship surgeon to Boston in a line of ships which took out emigrants and brought back cattle.

Medicine and even public health work never saturated all his energies, and when his health could not stand up to the rigours of industrial practice in Salford he turned to patenting some of his inventions—a tipping ashbin and a portable bath—till the first world war clamped down on these efforts. He then returned to practise in the rural north, and in the next few years evolved his theories for attacking unemployment and for opening up Cumberland, Westmorland, and Furness by a west-coast road, estimating with care the difficulties and costs of spanning the estuaries as would a civil engineer.

For holidays for many years he visited and charted stone-post circles in the British Isles, and on his retirement to the Isle of Man he settled down to the work of writing his conclusions of man's evolution, wanderings, and settlements. Further, from the age of 76 onwards, he alternated this work with the active creation of a home and garden from a ruined mill, of which his descendants are justly proud.

His chronological age was 100 years, but his alert mind was more like 50 years, as old friends and patients appreciated to the last weeks of his life.

R. HANDLEY GREAVES, M.B., Ch.B.

Dr. R. Handley Greaves died on November 11, 1959, in Sheffield, where he had practised for many years. He was 63 years of age.

Robert Handley Greaves was born at Sheffield on February 23, 1896, the elder son of Dr. Robert Bond Greaves. He was educated at King Edward VII School, Sheffield, and Sheffield University, where he graduated M.B., Ch.B. in 1919. After qualification he held the appointments of house-physician and house-surgeon at the Royal Infirmary, Sheffield. During the first world war he served as a surgeon lieutenant in the R.N.V.R. in H.M.S. *Tyrant*. On release from the Navy he took over the family practice in Sheffield in partnership with his brother, Dr. Cyril Handley Greaves.

Robert Handley Greaves was a man of wide and varied interests, but his greatest concern was the building up of Christ's Kingdom on earth, and during the past twenty-five years he became more and more convinced of the place for Divine healing in a doctor's ministry. It was his desire that his patients should have complete health, and he sought to bring healing not only to body but to mind and spirit. He was a lifelong, devoted, and active member of St. Andrew's Parish Church, Sheffield, being churchwarden for the past twelve years. He was one of the few members of the Church of England who read the Old and the New Testaments in the original Hebrew and Greek. His sincere and selfless devotion to his patients remained to the end, for only a few days before he died, though critically ill, he would rise from his bed to attend to patients who came for immediate care and attention. He will be remembered by many as a faithful physician and true Christian gentleman.

Dr. Handley Greaves's wife died eight months before his death. He leaves two sons and two daughters.

WILLIAM McMULLAN, L.R.C.P.&S.Ed., D.P.H.

Dr. William McMullan, for many years a well-known general practitioner in Birmingham, died at his home in Moseley on December 14. He was 74 years of age.

William McMullan was born on January 1, 1885, at Banbridge, Co. Down. He studied medicine at Belfast, but his student career was interrupted by the first world war, during which he served with the Northumberland Fusiliers and the Durham Light Infantry. After qualifying in 1920 he worked for a time as assistant surgeon in the *Mauretania*. He took the D.P.H. at Liverpool in 1923, but his particular interest was in ophthalmology, and at one time or another he held clinical assistantships at the Royal London Ophthalmic Hospital, the Central London Ophthalmic Hospital, and Oxford Eye Infirmary. In 1922 he went into general practice in Birmingham, maintaining also an extensive ophthalmic practice. A member of Birmingham City Council from 1930 to 1945, he took a keen interest in local government affairs. He leaves a widow and a daughter, to whom we extend our deep sympathy.—W. L. G.

C. G. TOWNSEND, M.B., B.Chir., F.F.A. R.C.S.

Dr. C. G. Townsend, anaesthetist to the Dreadnought Hospital, Greenwich, and Memorial Hospital, Woolwich, died on December 19, 1959, as the result of a road accident.

Charles Geoffrey Townsend was born in Bristol in 1902 and educated at Brighton College, Sidney Sussex College, Cambridge, and Guy's Hospital. At Cambridge he rowed in his college boat and also represented Sidney Sussex in athletics, and at Guy's he rowed in the hospital eight. After qualifying in 1927 he held several resident appointments at Guy's and then graduated M.B., B.Chir. in 1929. He returned to Cambridge for a time as resident anaesthetist at Addenbrooke's Hospital, and in 1930 he went into general practice in Beaconsfield, continuing his work as an anaesthetist on the honorary staff of the King Edward VII Hospital, Windsor. During the second world war he worked as a specialist anaesthetist in the Emergency Medical Service, being attached to the Southern Hospital, Dartford. Later he became consultant anaesthetist to the War Memorial Hospital, Woolwich, and to the Dreadnought Hospital, Greenwich. He took the D.A. in 1942 and was elected F.F.A. R.C.S. in 1953.

S. E. B. writes: Dr. C. G. Townsend will be missed by all his colleagues, who will remember chiefly his quiet efficiency and imperturbability in the most trying circumstances. He was a stimulating companion and when he made a member of a party all regained the spirit of undergraduate days. He retained a great love of all forms of sport. He married in 1931 Margaret Daltry, of Guy's Hospital nursing staff, who survives him with his son and daughter.

HERBERT TOMLIN, M.D., D.P.H.

Dr. Herbert Tomlin, who had practised as an ophthalmic and ear, nose, and throat surgeon in Huddersfield since 1919, died in hospital on December 29, 1959, after a short illness. He was 78 years of age.

Herbert Tomlin was born in Barnsley on September 13, 1881, and studied medicine at the Leeds medical school, graduating M.B., Ch.B. at the Victoria University of Manchester in 1904. After house appointments at Leeds General Infirmary and Lincoln County Hospital, he married in 1907, and then entered general practice in the village of Shirebrook, Derbyshire. Between then and the outbreak of war in 1914 he found time to proceed to the degree of M.D. and to take the D.P.H. He also undertook part-time work in the specialty of ophthalmology, and was appointed honorary ophthalmic surgeon to the Mansfield Hospital. During the first world war he served as ophthalmologist with Northern Command and with No. 3 General Hospital in the B.E.F. He was awarded the Médaille de Epidémies by the French Government for his work on trachoma in Chinese labour camps in France.

In 1919 he went to Huddersfield and started a consultant ophthalmic and E.N.T. practice in that town and in Barnsley, holding appointments as surgeon at the Kendray Hospital, Barnsley, the Mirfield Memorial Hospital, and, later, the Deanhouse E.M.S. Hospital. He was at one time school oculist to the West Riding, Huddersfield, and Barnsley education authorities. After the second world war, during which he was a major in the Home Guard, he enjoyed serving as member and chairman of the ophthalmic services committee of the Huddersfield executive council. He had been a member of the B.M.A. for nearly half a century, and was vice-chairman of the Huddersfield Division in 1928 and chairman from 1929 to 1930, a member and past-president of the Huddersfield Medical Society, and a member of the North of England Ophthalmological Society and the Leeds and West Riding Medico-chirurgical Society.

Apart from his professional work, he became a well-known figure in Huddersfield. A good mixer, a witty speaker, an amateur viola player, and a keen golfer, he had a wide circle of friends. At one time he was a member of no fewer than ten local clubs or societies which had social, cultural, or recreational objectives, and to each he found time to give his personal support and help.

Herbert Tomlin will perhaps be longest remembered for his unrecorded and often unexpected acts of kindness to friends, acquaintances, and strangers. Although a specialist, he retained throughout his life much of the broad outlook of the general practitioner, and he was by nature a psychologist. Many turned to him in time of trouble, and received good advice. He continued working until a week before his death from a cerebral haemorrhage, and had performed his last minor operation only two weeks earlier. At his funeral service he was described as "one who loved his fellow men."

W. G. V. SAID, M.D.

Dr. W. G. V. Said, who was a general practitioner in Preston, died on December 29 at the age of 49.

Walter George Vincent Said was born in Malta on January 11, 1910. He graduated in medicine at Malta University in 1934, coming to London shortly afterwards to take a course in tropical diseases. He later went to Yorkshire, where he held various assistantships. Not long after his marriage in 1938 he bought a practice in Preston, working there until his death. At the outbreak of the second world war in 1939 he joined the R.A.M.C., and during his service he spent some years in Malta, where he saw and endured the hardships of that sorely tried George Cross island.

M. J. F. writes: I met Walter Said first on his return to civilian life in 1946, when, like others in a similar position, he had to start reviving what was left of his practice. With the assistance of medical boards he was soon on his feet again and began to take an active part in local medical politics. He was a member of the B.M.A., a founder member of the College of General Practitioners, a member of the local medical committee from 1948 until his death, and a member of the Guild of St. Luke, SS. Cosmas and Damian, of which he was at one time treasurer. As a devout Catholic he took a great interest in the work of the guild. All our sympathy goes out to his widow and two children.

F P. BENNETT, M.R.C.S., L.R.C.P.

Dr. F. P. Bennett, who practised for many years in Kilburn, died on December 30, 1959, at the age of 88.

Frank Percy Bennett was born in Birmingham on May 21, 1871, and was educated at the Grammar School, Burton-on-Trent, St. David's College, Lampeter, University College, Cardiff, and St. Mary's Hospital, London, which he entered with a scholarship in natural science in 1908. Soon after qualifying in 1914 he went into general practice in Kilburn.

P. H. R. writes: I first got to know Dr. F. P. Bennett in 1948, when I began to assist him and shortly afterwards to work in partnership with him. A rationalist in outlook, he was kind and sympathetic and very careful in all his work. He was beloved by all his patients, who missed him greatly when he retired in 1953. Our sympathy is extended to his wife and daughters.

E. E. MATHER, B.M., B.Ch.

The obituary of Dr. E. E. Mather was published in the *Journal* of December 26, 1959 (p. 1489).

J. L. writes: The second world war placed a great strain upon Dr. E. E. Mather, and caused a relapse of the illness he sustained when suffering the privations of a prisoner of war in the first world war. He fought this illness with great courage, and eventually resumed Ministry work until his sudden death. He was well beloved throughout the whole district, and patients never ceased to visit him and inquire after him when he retired.

Medico-Legal

POSING AS DOCTOR

[FROM OUR LEGAL CORRESPONDENT]

On December 15 Douglas Paul Jones, of Church Inn, Mynyddislwyn, pleaded guilty to charges arising out of his posing as a qualified medical practitioner (*Yorkshire Post*, December 16). Jones was tried in the Magistrates' Court at Merthyr Tydfil on four charges: that he obtained 16 guineas from a Dr. Mangan by falsely pretending to be a qualified medical practitioner; that he falsely pretended to be a Bachelor of Medicine; that he wilfully made a false certificate under the Births and Deaths Registration Act, 1953; and that he procured a drug or preparation (pethidine) without being generally licensed or authorized to do so.

Jones, who was aged 29, had had thirteen different jobs, including that of miner, shop assistant, seaman, and farm labourer. When out of work in September, Jones overheard in a conversation that a doctor in Merthyr Tydfil was looking for a locum. He got in touch with the doctor and worked with him for six days, and then worked alone for another fortnight, after the doctor had gone away on holiday. Jones made out 800 prescriptions, including 6 for dangerous drugs and 203 for scheduled poisons. When he was in the surgery he copied out prescriptions from those previously recorded on the patients' cards. He also became engaged to the daughter of one of his patients. Jones left the district as the result of his fright after being called upon to examine a dead body and sign a death certificate. There was no complaint that any patient had suffered as a result of his treatment.

Jones was put on probation for two years on condition that he resided at an institution for treatment for not more than one year.

Medical Notes in Parliament

MR. PAGE'S ROAD SAFETY BILL

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Rarely can a B.M.A. report have made such a timely appearance as the revised *Relation of Alcohol to Road Accidents*.* Its publication came only a day after the text of the Road Safety Bill introduced by Mr. GRAHAM PAGE, Conservative Member for Crosby and chairman of the Pedestrians Association. Both have appeared—though neither was instigated by it—when public opinion has been more than usually stirred about road injuries and deaths by the Christmas toll.

The report says (with some reservations for individual characteristics) that in the driver of a motor vehicle a concentration of 50 mg. of alcohol in 100 ml. of blood is the highest that can be accepted as consistent with the safety of other road users. The Bill would make it an offence for any person who has 150 mg. or more of alcohol in 100 ml. of his blood to use a road vehicle.

"Road Using after Taking Alcohol"

The operative clause is the first of four which constitute new road offences. (The others are of a quite different order—turning right without warning, inability to stop within distance of vision, and overtaking within 45 ft.—13.7 m.—of a pedestrian crossing.) Clause 5 ("Road Using after Taking Alcohol") declares, first, in subsection (1), that "any person who (*a*) when using or attempting to use, or when in charge of a vehicle on a road or other public place, or (*b*) when unaccompanied upon a carriageway, has 0.15% or more by weight of alcohol in his blood shall be guilty of an offence," and liable on summary conviction to a maximum fine of £50 or up to three months' imprisonment, and for a second or subsequent conviction to maximum penalties of £100 or three months' imprisonment, or both. It also makes the offence subject to the disqualification provisions of the 1956 Road Traffic Act. For the purpose of the clause a person—that is, "any person"—is defined as being unaccompanied if he is not in company with another over the age of 16 years and who has less than the prescribed amount of alcohol in his blood.

Powers of Police

The clause proceeds to give wide powers to the police. Subsection (4) states: "A police constable in uniform may arrest without warrant any person whom he has reasonable cause to believe is committing an offence under subsection (1), and any police constable may, when a person so arrested is within a police station, require him to submit to such medical, chemical, and clinical tests involving exhalation of breath and urination as may be prescribed from time to time . . . and in order to ascertain by instruments or chemical reactions the alcoholic content of a person's blood." Subsection (5) adds to this that "Any person who wilfully refuses to comply with the requirement of a police constable given in accordance with the last foregoing subsection shall be guilty of the offence of obstructing the police constable in the course of his duty unless the person shall submit to an extraction by a qualified medical practitioner of sufficient blood from his body to permit a chemical analysis to ascertain the alcoholic content thereof."

Another subsection relates these provisions to the offences of driving or being in charge of a motor vehicle when under the influence of drink or drugs, contained in the Road Traffic Acts of 1930 and 1956, and states that any information obtained under subsections (4) and (5) may be adduced in evidence at a trial.

Bill's Other Objects

The Bill has other objects, too. It would authorize the establishment of a Road Safety Commission and corps, in addition to the police force, with powers and duties relating to the preservation of the safety of road users and the control of vehicles and pedestrians, as prescribed by the Home Secretary. It also seeks to stiffen the penalties for a wide variety of existing traffic offences, including an extended use of disqualification for varying periods up to a minimum of six months for road-using after taking alcohol, and a minimum of 12 months for driving or being in charge of a motor vehicle when under the influence of drink or drugs.

Back-bench Legislation

It must be remembered that this is a private Member's Bill. As such it is subject to the hazards which beset all legislative efforts by back-benchers. These are mainly procedural, given the support of a sufficient majority, and are in substance limited opportunity for further progress. Mr. Page's Bill would appear to face two substantial obstacles—its ambitious scope, and the prospect of an early Government Bill on road safety. It appears from its contents to be well beyond the usual conventions of private members' legislation, and it is doubtful whether the House would accept such drastic powers on the authority of a back-bencher, who would be responsible for the exceedingly onerous duty of piloting it through its subsequent stages.

It is even more doubtful whether the Government would advise the House to accept it, even were they not themselves engaged on matters with which it seeks to deal. For this Bill has been largely overtaken by events since it was announced last November. In so far as it deals with traffic offences of the ordinary kind—licensing, road conduct, condition of vehicle, and so forth—a new Minister of Transport has already made the running in a speech which indicated the importance he attached to the enforcement of

*Brit. med. J., 1960, 1, 269.

existing legislation. Both he and the Home Secretary have looked favourably on the idea of traffic wardens, although not exercising the wide authority that Mr. Page would probably arm them with. Apart altogether from the desirability of compulsory blood and breath tests by the police, made on "any person" using the highway and suspected of being under the influence of alcohol, which would itself be a highly controversial issue, the very topicality of this back-bench measure could be sufficient to cause its own undoing.

A Government Bill

Mr. Page and his supporters would no doubt feel their work sufficiently rewarded if their purpose and some of their ideas were to be embodied in a Government Bill which the Home Secretary has promised "quite soon." The B.M.A. Committee also would be more quickly repaid for their labours than most expert bodies if their findings became the basis of early action.

The real interest in the second reading debate on this Road Safety Bill, which is the second measure to be discussed on February 5, and therefore will have appreciably shorter time for debate, will be the extent to which it draws from the Government some indication of their own thinking on the alcoholic factor in driving, and their own proposals to promote road safety.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on December 12, 1959, the degree of M.Chir. was conferred, by proxy, on P. P. Philip.

UNIVERSITY OF ST. ANDREWS

At a Graduation ceremonial on January 8 the following degrees were conferred:

PH.D.—*In the Faculty of Medicine:* D. N. Sharma, M.B., B.S. (*in absentia*).

M.B., CH.B.—Mary R. Bestow, Catherine D. Campbell, B. C. Davies, Doreen Wilson (or Eldred), A. M. Gough, S. W. Gray, A. B. A. Grubb, J. Lawless, G. A. Nimberg (*in absentia*), R. C. Waters, A. Woldesemait.

UNIVERSITY OF GLASGOW

The following degrees were conferred on January 16:

M.D.—[1]A. P. Curran, [2]E. McC. McGirr, [1]R. Rankine, [2]R. G. Sommerville, [1]Morag C. Timbury.

CH.M.—[1]D. W. Short.

PH.D.—G. C. Arneil, M.D.

M.B., CH.B.—J. G. Bisset, J. T. Breen, J. M. Carlisle, T. A. H. Hide, E. J. N. Hoisington, J. Kelly, A. King, J. L. Kydd, C. Lynch, Margaret M. McNamara, G. L. Miller, G. A. Montgomerie, J. Newlands, T. P. Orr, P. Palmer, W. H. Pitt, T. Prior, G. D. Ross, L. L. Venkatasawmy, Jean M. West (née Irvine), Hannchen D. Wirth, and, *in absentia* by diploma, Y. Black.

[1]With commendation. [2]With honours.

Bellahouston medals for eminent merit in theses submitted in 1959 for the degree of Doctor of Medicine have been awarded to: W. A. J. Crane, J. Crooks, and A. J. S. McFadzean.

UNIVERSITY OF ABERDEEN

The University Court has appointed Dr. Ian Brenton Porteous to a terminable Lectureship in Pathology, from January 25, 1960.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College held on December 18, 1959, with Professor John Bruce, President, in the chair, the following candidates were admitted Fellows without examination: A. H. Jacobs, President of the Royal Faculty of Physicians and Surgeons of Glasgow, V. C. Rambo, J. D. Wade.

S. Plumpton, M.B., Ch.B., F.D.S. R.C.S., was elected a Fellow in Dental Surgery without examination.

The following candidates who have passed the requisite examinations were admitted Fellows:

J. B. Anchen, B. J. Bowden, B. C. Bracken, M. N. Brahma, D. P.-C. Chan, R. D. Char, G. D. Chisholm, E. P. H. Chu, E. C. Cowan, A. C. B. Dean, L. C. Dutta, A. M. Gokarn, P. A. Goodwin, C. E. Graham, E. C. G. Lee, B.-C. Gupta, S. D. Holloway, M. Huq, A. R. Isaac, G. R. James, V. V. Kayarkar, J. A. Kennedy, I. F. Kerr, K. G. Kling, I. Labuschagne, W. M. L. Laubscher, H. I. Leigh, P. J. Lethlean, J. H. Lowry, A. W. R. Mabrouk, J. G. Mathie, B. Measday, M. P. A. Menon, K. K. Merten, W. G. Millar, J. C. Milliken, S. M. Monif, J. Morgan, J. Norman-Smith, T. G. O'Donovan, T. A. Paraman, P. Paramaswaami, P. R. Payne, R. S. Phillips, M. M. Rao, W. H. Reid, V. Romanowski, S. Shanmugam, I. D. Sood, R. W. Springhall, J. Tevendale, R. N. Tinning, M. A. Turner, M. P. Vaidya, M. Waliuddin, A. B. Young.

D. C. Hall, M.B., Ch.B., L.D.S. R.C.S., having passed the requisite examination, was admitted a Fellow in Dental Surgery.

UNIVERSITY OF LONDON

Dr. D. L. J. Bilbey, assistant professor of anatomy in the University of Toronto, and Dr. R. M. H. McMinn, lecturer in the University of Sheffield, have been appointed to Readerships in Anatomy tenable at King's College.

The following degrees were awarded in December, 1959:

M.D.—A. M. Dawson, P. J. Koblenzer, A. C. K. Lawrence, I. Macdonald, J. Burston, J. D. Pryce.

PH.D.—*In the Faculty of Medicine:* M. J. Davey (Chelsea College of Science and Technology), K. R. V. R. Ghorpade (London Hospital Medical College).

The following have been appointed, reappointed, or renominated as representatives of the University on the governing bodies indicated in parentheses: Sir Francis Fraser (Board of Management of the London School of Hygiene and Tropical Medicine) and Mr. R. C. Davenport, Dr. Katharine G. Lloyd-Williams, and Professor A. A. Moncrieff (Court of Governors of the London School of Hygiene and Tropical Medicine).

UNIVERSITY OF BIRMINGHAM

Dr. R. F. Fletcher has been appointed Lecturer in Medicine.

UNIVERSITY OF BRISTOL

The following candidates have been approved at the examinations indicated:

FINAL M.B., CH.B.—R. I. A. A. Aubee, J. A. G. Benson, G. C. Duff, H. W. Haskins, D. R. M. Heighton, J. P. A. Hill, R. C. Hodge, G. W. E. Lockett, Madeline D. Mayne, D. T. H. Randell, Dorothy M. I. Sibbald, D. J. Stayte, Madueke Ugwunze, R. J. Undugodage. *Group I* (completing the examination): K. R. Davies, G. Kerr.

M.D.—T. J. Butler (with distinction), C. C. Downie, J. E. Tovey.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on January 14, with Sir James Paterson Ross, President, in the chair, Mr. L. J. Williams was admitted to the Court of Patrons.

Professor A. W. Wilkinson was admitted to the Fellowship *ad eundem*.

Diplomas were granted, jointly with the Royal College of Physicians of London, to the following successful candidates:

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—U. O. Ali, S. K. Ally, G. P. E. Beaney, L. Bernstein, P. R. Blenkinsop, D. J. Durcan, Muriel E. Gibb, S. K. Guha, D. G. Jones, J. G. Kourris, R. P. Kumar, G. J. Little, R. S. McAlary, W. J. O'Connell, I. Parhizgar, A. S. Shalom, O. T. Taylor, C. I. Woolf.

DIPLOMA IN ANAESTHETICS.—R. St. J. Angel, R. G. Asghar, A. V. Bal, Shirley B. Barker, R. S. B. Bennett, A. I. Booth, J. P. Broad, J. M. B. Burn, N. T. A. Byam, Anne L. Campbell, F. N. Campbell, J. Ll. Canton, Charlotte L. K. Christie, Doris W. Cole, Maeve S. Counihan, J. W. Crooke, Eileen M. Darwood, T. C. Dixon, M. P. Dowdell, I. S. du Toit, H. B. Edghill, Pamela E. Fancourt, D. J. Foley, Ann F. Gamble, June S. Grant, A. M. Hall-Smith, Pamela C. Harrison, J. J. Hazlett, Hla Tun, R. F. Hunt, J. L. Hunter, Elizabeth M. Irvine, K. C. B. James, F. W. Jones, V. R. Keep, Anne H. Kinnell, O. Krishna, W. van der M. Lambrechts, Doreen J. Leckie, Muriel F. Lehane, D. B. Longson, B. M. Lottering, Elizabeth M. B. McKenzie, K. C. Mathur, J. A. Monro, J. D. Muir, J. J. Mulcahy, P. C. Murray, Pamela M. Mylward, S. S. Nadkarni, B. G. Nanji, M. A. Ness, Elizabeth M. Nicholson, M. P. O'Dwyer, Sheila M. Power, P. N. Rastogi, Marian J. Rice, K. W. Ridings, D. S. Robertson, Audrey F. Rogers, S. Roy, Vivienne Schein, H. G. Schroeder, M. D. Scott, Sein Sein Khin, G. K. Singh, D. H. Sivadevaiah, Janet M. Spencely, Pamela J. Stow, M. B. Teal, J. G. Teall, A. T. Thomason, Elizabeth M. T. Thyne, B. le G. Waldron, Edith J. Wilson, Kathryn M. Wilson.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—S. Al-Fakhri, M. A. Bloomfield, A. L. Brown, Stephanie J. Carter, K. W. Chow, J. O. M. C. Craig, J. W. Davidson, H. F. Davies, S. Elk, N. Geffen, A. G. Giddins, J. B. Howells, Don L. N. Jayawardena, R. Kayaleh, I. H. Kerr, J. J. Key, C. D. Krasner, R. N. Kundu, E. M. McIlrath, R. H. Mackay, L. R. MacLean, L. Mak, G. F. Mayall, M. I. M. Nilar, R. A. Owen, L. H. Pell, T. Rajcoomar, M. F. Shellshear, J. B. Simmons, Elizabeth M. Sweet, D. H. Trapnell, H. P. Tulloh, M. J. Turner, P. J. De La R. Van Wijk, H. R. Watson-Baker, Vivienne C. P. Wong, J. C. K. Yin.

DIPLOMA IN MEDICAL RADIOTHERAPY.—M. T. Aung, Daphne I. L. Dacosta, S. K. Dharmalingam, R. G. B. Evans, H. T. Ford, Emma Mukherjee, P. Nilprabhassorn, J. P. Perry, Urmil Sikand, Mary E. G. Skinner, B. C. Tan, Y. K. Tan, M. M. Tint.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—G. M. Baird, R. Banerjee, D. E. H. Beattie, R. C. Benians, R. G. Bird, V. H. A. Black, J. P. Bomford, Anne N. M. Brittain, R. A. Brookes, Dorothy L. N. Brown, Elizabeth F. Browne, D. M. Carter, J. A. Chapman, L. G. Cottrell, G. O. Cowdy, E. W. Davies, J. D. Denford, A. W. Drummond, H. Eaton,

A. Esterson, C. I. Finn, I. G. Fitz-Patrick, Joyce M. Galbraith, R. S. Gillen, L. J. Glancy, N. Gold, Elizabeth A. Green, J. A. Gumbrell, Christina McI. Hamilton, J. A. Harris, A. R. Jones, N. Kaye, A. V. de P. Kelly, J. Le Gassicke, Janet M. M. Lindsay, D. L. M. McNeill, J. B. McWhinnie, Barbara G. Meyler, R. T. F. Moloney, M. C. Moss, R. Neville, C. O. Oshodi, P. L. Parsons, A. Pearce, T. P. S. Powell, D. J. Power, V. S. Rastogi, M. J. Sainsbury, J. F. Scott, R. W. Smith, R. E. Steel, C. D. Thomson, K. J. Tilling, G. C. Timbury, N. A. Todd, H. P. Tollinton, Nancy M. Tweedie-Stodart, D. S. Vorster, D. G. A. Westbury, M. T. C. Wright, N. Wright, L. M. Zinkin.

DIPLOMA IN PATHOLOGY.—M. D'A. Crawfurd, J. A. McMillan, A. S. Mohamed, K. Posney, Dona P. Wijesinghe.

DIPLOMA IN PUBLIC HEALTH.—M. W. Beaver, P. K. Biswas, C. Boonmark, J. K. Butterfield, C. Cassar, H. A. Collins, Dorothy M. Edwards, C. O. Foenander, F. W. Ford, R. McK. Laslett, Sushila Maity, A. A. Opara-Nadi, S. E. Nii-Amu Otoo, D. G. H. Patey, B. A. Roberts, O. A. Soboyejo, Anne Q. C. Tay, Anne M. Timmis.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—T. W. Brown, D. H. Cook, A. Hadjian, Tanvir Islam, A. D. Laud, L. W. Padgett, R. Scott, V. Shaikh, G. R. Thompson.

DIPLOMA IN CHILD HEALTH.—E. G. Mendis.

Vital Statistics

Provisional Figures for 1959

The Registrar-General has issued provisional figures of the main vital statistics for England and Wales for the last quarter of 1959 and for the year as a whole. During the quarter there were 173,390 live births (178,382 in the same quarter of 1958), 3,572 (4,056) stillbirths, 127,119 (133,450) deaths, and 3,926 (4,093) deaths of infants under 1 year. In 1959 the live birth rate was 16.5 per 1,000 population, the highest since 1948; the stillbirth rate was 20.7 per 1,000 total live- and stillbirths (21.6 in 1958); the death rate was 11.6 per 1,000 population (11.7 in 1958); and the infant mortality rate was 22 (22.6 in 1958 and 32.4 in 1949).

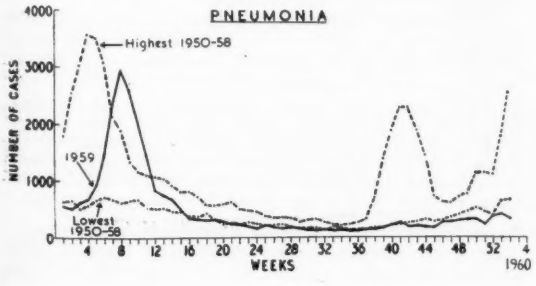
The natural increase of the population (excess of births over deaths) in 1959 was 222,596, the largest figure since 1948, when it was 307,072.

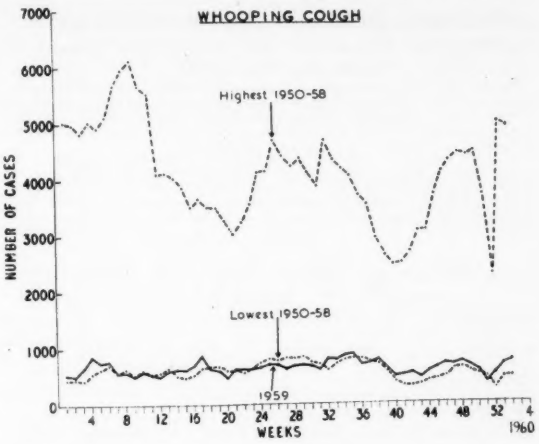
Venereal Diseases

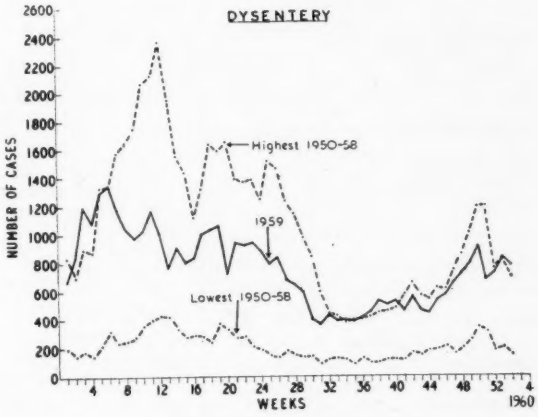
In England and Wales during the quarter ending September 30, 1959, 960 new cases of syphilis were reported as attending the clinics, as compared with 1,032 the previous year. Of these, 205 were classified as primary, secondary, or latent in the first year of infection. Five cases of congenital syphilis in children under 1 year were reported, and 83 cases in persons over that age. New cases of gonorrhoea (with corresponding 1958 figures in parentheses) numbered 9,224 (7,986), of chancroid 57 (65), and of non-gonococcal urethritis (males only) 5,952 (5,197).—*Monthly Bulletin of the Ministry of Health*, December, 1959.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus - - - - - -, the figures for 1959–60 thus ———. Except for the curves showing notifications in 1959–60, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Jan. 9	Week Ending **Jan. 16**
Whooping-cough		
Warwickshire	41	**71**
Birmingham C.B.	15	**24**
Coventry C.B.	8	**36**
Acute Poliomyelitis		
London	1	**2**
Essex	0	**2**
Norfolk	0	**2**
Wayland R.D.	0	**2**
Staffordshire	0	**2**
Wolverhampton C.B.	0	**2**
Yorkshire West Riding	1	**2**
Dysentery		
Durham	12	**27**
Lancashire	198	**222**
Bolton C.B.	25	**31**
Liverpool C.B.	27	**28**
Preston C.B.	23	**31**
Oldham	6	**11**
Swinton and Pendlebury M.B.	30	**25**
Wiltshire	7	**42**
Cricklade and Wootton Bassett R.D.	7	**37**
Glasgow	117	**126**
Diphtheria		
London	0	**3**
Camberwell	0	**2**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 9** (No. 1) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	5	0	2	0	4	5	1	5	0	3
Dysentery ..	840	174	211	6	9	675	51	174	6	3
Encephalitis, acute	3	1		0		3	1		0	
Enteric fever:										
Typhoid ..	2	1	1	0	1	1	1	0	0	
Paratyphoid ..	7	0	0	0	1 (B)	9	1	3 (B)	0	
Food-poisoning ..	134	24	29	0		148	23	8	2	
Infective enteritis or diarrhoea under 2 years				14	22				11	20
Measles*	1,407	17	26	16	7	15,129	1068	251	114	689
Meningococcal infection	19	4	11	0	1	25	1	16	0	2
Ophthalmia neonatorum	16	2	5	0		27	8	8	0	
Pneumonia† ..	420	21	307	2	9	550	45	405	13	2
Poliomyelitis, acute:										
Paralytic ..	2	0	0	} 0		{ 26	} 1	1	0	1
Non-paralytic ..	2	1	0			{ 17				
Puerperal fever§ ..	189	26	9	1		210	41	7	0	
Scarlet fever ..	800	38	145	24	21	769	47	73	27	16
Tuberculosis:										
Respiratory ..	397	51	53	16		467	56	74	14	
Non-respiratory	54	2	6	5		52	2	6	2	
Whooping-cough	667	74	121	11	79	529	18	70	116	69

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	1
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		1	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	1	0	0	10	0	2	0	1
Influenza	34	2	4	0	1	41	3	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				1	0		
Pneumonia ..	614	47	21	11	10	773	74	37	19	19
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 79	{ 0	8	1	5	} 100	{ 11	13	3	5
Non-respiratory		{ 1	0	0	1		{ 0	0	0	1
Whooping-cough	0	0	0	0	1	0	0	0	0	0
Deaths 0–1 year ..	325	46	22	9	12	361	28	35	12	17
Deaths (excluding stillbirths) ..	10,908	848	730	173	184	11,871	984	833	178	215
LIVE BIRTHS ..	15,587	1288	1312	266	329	15,405	1417	1255	263	431
STILLBIRTHS ..	289	19	27			372	49	31		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Medicine Laws to be Examined

The Minister of Health, in consultation with the Home Secretary and the Secretary of State for Scotland, has set up an Interdepartmental Working Party "to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalize and simplify the law with a view to ultimate amendment and consolidation."

The statutes which the Working Party will consider include: The Venereal Disease Act, 1917; The Pharmacy and Poisons Act, 1933; The Cancer Act, 1939; The Pharmacy and Medicines Act, 1941; The National Health Service Act, 1946; The National Health Service (Scotland) Act, 1947; The Radioactive Substances Act, 1948 (Section 3); The Dangerous Drugs Act, 1951; The Food and Drugs Act, 1955; The Food and Drugs (Scotland) Act, 1956; The Therapeutic Substances Act, 1956; and The Medical Act, 1956 (Section 47).

B.S.I. and Dangerous Toys

The British Standards Institution is setting up a technical committee to draw up a set of recommendations on safety aspects in the manufacture of toys. This move follows the publication last year of a report on dangerous toys by the National Affairs Committee of the Portsmouth Chamber of Commerce.

The report, *Danger at Play*, found that 138 (41%) out of some 336 children had had accidents caused by toys. (See *Journal* annotation, May 2, 1959, p. 1173.) The B.S.I. committee is also to consider the possibility of a British Standard for babies' rattles with a view to limiting the types of material which are used to provide the rattling noise, and to making the contents more inaccessible.

Finding Homes for the Aged

Since the war an increasingly popular solution to the problem of accommodation for elderly people who have nowhere suitable to live is boarding them out with private families. To guide those who want to start a similar scheme in their own area, the National Old People's Welfare Council has published *Boarding-out Schemes for Elderly People* (price 1s. 6d.), which gives useful advice, based on experience, on how to set about it, and includes an appendix of information compiled from voluntary boarding-out schemes in various parts of the country.

Royal College of Surgeons, England

At a meeting of the College Council on January 14 the following awards and appointments were made:

Mr. H. J. SEDDON (Robert Jones Lectures); Professor FERNAND ORBAN (Moynihan Lectureship); Mr. G. D. ROBB, Commonwealth Travelling Professor (College Lecture); and Dr. R. P. W SHACKLETON (Frederic Hewitt Lectures for 1961).

North of England Obstetrical and Gynaecological Society

The following have been elected officers for the year:

President: Professor T. N. A. JEFFCOATE; *vice-presidents:* Mr. J. B. FARQUHAR (Leeds), Sir ARTHUR GEMMELL (Liverpool), Miss E. M. MILLS (Manchester); Mr. J. M. KING (Newcastle), Mr. J. A. HADLEY (Sheffield); *honorary treasurer:* Mr. T. B. FITZGERALD; *honorary general secretary:* Mr. H. V. CORBET; and *honorary reporting secretary:* Miss U. M. LISTER.

Marriage Guidance Council's Appeal

The Marriage Guidance Council hopes to raise £250,000 to expand the Council's work during the next 10 years; £45,000 of this sum is needed to cover the cost of a move to more spacious premises.

Lord KILMUIR, who launched the formal appeal for funds, pointed out that the taxpayer found about £1m. a year for legal aid for those who could not afford the cost of divorce proceedings, and said that "it is beyond doubt that in marriage guidance efforts to prevent or overcome the breakdown of marriages and homes we are striking at the taproot of juvenile delinquency."

World Population and Planned Parenthood Appeal

The International Planned Parenthood Federation has launched an appeal designed to raise £250,000 in Britain

in a year. The proceeds will be spent mainly in the under-developed countries of the Near and Far East, in Africa, India, Pakistan, and Ceylon.

In addition to educating people about birth control, the Federation gives advice on fertility, and, in regions where there are no independent marriage guidance councils, it undertakes this task as well.

Group for Representation of the Views of Clinical Psychiatrists

The new Secretary of the G.R.V.C.P., which was formed at the end of last year (see *Journal*, December 5, 1959, p. 1269), is Dr. B. C. GILSENAN, Shenley Hospital, near St. Albans, Hertfordshire, to whom all communications should be addressed.

Extension to Glasgow Royal Mental Hospital

An extension to Glasgow Royal Mental Hospital—the first of its kind in Scotland since the beginning of the National Health Service—was opened recently by Sir DAVID HENDERSON.

[*Annan Photographer Glasgow*

The two-story building, which is shown here, cost over £100,000, and provides 80 beds for women patients in eight six-bed dormitories and 32 single rooms, in addition to the usual offices and visitors' waiting-rooms.

B.M.A. Report on Alcohol and Accidents

The report of the British Medical Association's Special Committee, *Relation of Alcohol to Road Accidents*, which was published last week (*Journal*, January 23, p. 269), is obtainable from the Publishing Manager of the Association, B.M.A. House, Tavistock Square, London, W.C.1. The price of the report is 2s. 6d. (2s. 10d., including postage), but no charge is made to members of the Association.

British Postgraduate Medical Federation

Sir JAMES PATERSON ROSS, P.R.C.S., has been appointed to succeed Sir FRANCIS FRASER as Director of the British Postgraduate Medical Federation when the latter retires on October 1.

People in the News

Professor JOHN LOEWENTHAL, who worked for a year after the war under Sir JAMES PATERSON ROSS, P.R.C.S., at St. Bartholomew's Hospital and who is now professor of surgery at Sydney University, is visiting Britain for a month, and has been invited by Sir James to take charge of his surgical unit at Bart's during his stay.

Dr. J. SHARP GRANT, medical officer of British Railways, Eastern Region, has been appointed chairman of an independent commission which is to inquire into the Rhodesia Railway Medical Fund.

Dr. A. J. MARSHALL, D.Phil., D.Sc., reader in zoology and comparative anatomy at St. Bartholomew's Hospital Medical College, London, is to be the first professor of biology at Monash University, the newly established university in Victoria, Australia.

"Family Doctor"

The February issue of *Family Doctor* is now available, price 1s. 6d. In an article called "The Facts about Fluoridation," Dr. G. WYNNE GRIFFITH says: "If we were all to revert to more natural foods and feeding habits, everyone's teeth would be sure to improve. During the war, when sugar was rationed and sweets difficult to obtain, children's teeth were much healthier than they are to-day."

COMING EVENTS

Assurance Medical Society.—General meeting, February 3, 4.45 p.m., Medical Society of London, 11, Chandos Street, Cavendish Square, London, W.1, followed by discussion on "Doubtful Cases."

Birmingham and Midland Medical Art Society.—First exhibition, Medical Institute, 36, Harborne Road, Edgbaston, Birmingham, 15, February 10 and 11, 6.0 p.m.–9.0 p.m.

London University. — Professor JOHN LOEWENTHAL (professor of surgery, Sydney University): "Some Contributions to Surgical Research," February 19, 4.45 p.m., Clinical Lecture Theatre, St. Bartholomew's Hospital, West Smithfield, London, E.C.1. Admission free.

Medical Art Society Exhibition.—March 4–17, Walker's Galleries, New Bond Street, London, W.1. Honorary Secretary: Dr. A. M. RACKOW, Fourways, Windy Ridge Close, Wimbledon, London, S.W.19.

National Association for Maternal and Child Welfare.—Annual Conference, Civic Centre, Bristol, June 22–24. Sessions include "Perinatal Mortality," "A Child and Family Guidance Service," "Handicapped Children," and "Problems of Adolescence." Details from the association, Tavistock House North, Tavistock Square, London, W.C.1.

International Congress of Gastroenterology.—Leyden, April 20–24, 1960. Details from Dr. C. SCHREUDER, 16, Lange Voorhout, The Hague, The Netherlands.

1st Czechoslovakian Congress of Paediatric Surgery.—Prague, May 23–25, 1960. Details from the Congress Office, 2, Ke Karlovu, Prague 2, Czechoslovakia.

NEW ISSUES

Archives of Disease in Childhood.—Issued bi-monthly (£4 4s. annually). The new issue (Vol. 34, No. 177) includes:

THE MAINTENANCE OF STABILITY IN THE NEWLY BORN. PART I. CHEMICAL EXCHANGE. R. A. McCance.
THE RELATIONSHIP BETWEEN CALCIUM-PHOSPHORUS METABOLISM, THE "KREBS CYCLE" AND STEROID METABOLISM. Ettore de Toni, jun., and Sergio Nordio.
FAMILIAL VITAMIN D-RESISTANT RICKETS. C. P. Dancaster and W. P. U. Jackson.
ELECTROPHORETIC STUDIES OF SERUM PROTEIN PATTERNS IN NEWBORN INDIAN INFANTS. B. S. Kulkarni, R. S. Satoskar, M. N. Parikh, and R. G. Chitre.
TETANUS IN AFRICAN CHILDREN. A. B. Tompkins.
THREE CASES OF NIEMANN PICK'S DISEASE IN CHILDREN. W. I. Forsythe, E. F. McKeown, and D. W. Neill.
A STUDY OF CONGENITAL HEART DEFECTS IN MONGOLISM. M. C. Liu and K. Corlett.
THE ELECTRICAL CONDUCTIVITY OF ELECTROLYTES FOUND IN THE SWEAT OF PATIENTS WITH FIBROCYSTIC DISEASE OF THE PANCREAS. Allan Bloxsom.
THE RELATIONSHIP BETWEEN DECREASED 5-HYDROXYINDOLE METABOLISM AND MENTAL DEFECT IN PHENYLKETONURIA. C. M. B. Pare, M. Sandler, and R. S. Stacey.
HONEYCOMB LUNGS WITH PERICHOLANGITIS. S. Sivanesan.
SPLENIC AGENESIS AND MULTILOBULATE SPLEEN. C. S. Muir.
BIRTH TRAUMA TO THE VERTEBRAL ARTERIES. P. O. Yates.
ACUTE INTESTINAL OBSTRUCTION DUE TO MESENTERIC LYMPHANGIOMA. B. M. L. Underhill.
A DESCRIPTION AND CLASSIFICATION OF THE COMMON DISORDERS OF SPEECH IN CHILDREN. T. T. S. Ingram.
BOOK REVIEWS.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 12) includes:

INFLUENCE OF THE INTRA-OCULAR PRESSURE ON THE FORMATION OF THE AQUEOUS HUMOUR AND THE OUTFLOW RESISTANCE IN THE LIVING EYE. M. E. Langham.
LAMELLAR KERATOPLASTY. D. Pierse and T. A. Casey.
USE OF THE ECHOGRAM IN THE LOCATION AND DIAGNOSIS OF INTRA-OCULAR FOREIGN BODIES. A. Oksala and A. Lehtinen.
POST-OPERATIVE MYCOTIC ENDOPHTHALMITIS DIAGNOSED CLINICALLY AND VERIFIED HISTOPATHOLOGICALLY. B. S. Fine and L. E. Zimmerman.
OCULAR METASTASIS FROM SEMINOMA. M. Garrett.
TRICHO-EPITHELIOMA OF THE EYELID. S. P. Mathur and B. P. Mathur.
TWO CASES OF CONJUNCTIVAL CYST. S. P. Mathur.
CONJUNCTIVAL AMYLOIDOSIS. S. P. Mathur and B. P. Mathur.
BOOK REVIEWS.
NOTES.
INDEX FOR 1959.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 11) includes:

FIBROSING RESPONSE TO AQUEOUS. ITS RELATION TO GLAUCOMA. E. Epstein.
BINOCULAR MECHANISMS IN SMALL-ANGLE STRABISMUS. A. Stanworth and D. da Cunha.
BINOCULAR DEPTH PERCEPTION IN SMALL-ANGLE STRABISMUS. E. J. Naylor and A. Stanworth.
BUFFERING TECHNIQUE FOR OBTAINING INCREASED PHYSIOLOGICAL RESPONSE FROM ALKALOIDAL EYE-DROPS. J. Boberg-Ans, K. V. Grove-Rasmussen, and E. R. Hammarlund.
LESIONS OF THE LID MARGINS CAUSED BY ECTOPARASITES IN INDIA. F. C. Rodger and H. U. Farooqi.
STUDIES ON DEVELOPING RETINAL VESSELS. VII. FLUORIDE-INDUCED VASO-OBLITERATION AND ITS RELATION TO RETINAL MATURITY C. Pedler.
ANAEROBIC GLYCOLYSIS IN RATS AFFECTED WITH RETINITIS PIGMENTOSA. P. T. Walters.
DARKROOM OUTFLOW TEST IN UNILATERAL CLOSED-ANGLE GLAUCOMA. W. S. Foulds.
VARIANT OF DUANE'S RETRACTION SYNDROME. H. Saiduzzafar.
BOOK REVIEWS.
NOTES.
OBITUARY.

British Journal of Industrial Medicine.—Issued quarterly (£3 annually). The new issue (Vol. 16, No. 4) includes:

POPULATION STUDIES OF CHRONIC RESPIRATORY DISEASE: A COMPARISON OF MINERS, FOUNDRY-WORKERS, AND OTHERS IN STAVELEY, DERBYSHIRE. I. T. T. Higgins, A. L. Cochrane, J. C. Gilson, and C. H. Wood.
SICKNESS ABSENCE AMONG RAILWAY CLERICAL STAFF. Derek S. Pugh, Cecil Gordon, and Katherine Lévy.
PNEUMOCONIOSIS IN CARBON ELECTRODE MAKERS. A. J. Watson, J. Black, A. T. Doig, and G. Nagelschmidt.
THE EFFECT OF DIFFERENT CONCENTRATIONS OF SILICIC ACID AND SILICA DUST ON THE BIOSYNTHESIS OF COLLAGEN IN TISSUE CULTURES. M. Chvapil and E. Holečková.
STUDIES ON THE NATURE AND AETIOLOGY OF RESPIRATORY DISABILITY IN WITWATERSRAND GOLDMINERS FREE OF RADIOLOGICAL SILICOSIS. Margaret R. Becklake, Saul Zwi, and W. Lutz.
AN ANALYSIS OF SOME OBSERVATIONS OF THERMAL COMFORT IN AN EQUATORIAL CLIMATE. C. G. Webb.
LATE CONSEQUENCES OF THE NEUROLOGICAL FORMS OF DECOMPRESSION SICKNESS. I. Rózsahegyi.
LUNG CANCER IN COAL-MINERS. R. Abbey Smith.
THE ORIGIN OF THE TERM ANTHRACOSIS. A. Meiklejohn.
MISCELLANEA:
A LABORATORY TRIAL OF SOME MODERN SCREENING TESTS FOR THE DETECTION OF GLUCOSE AND PROTEIN IN URINE. L. H. Turnbull.
OBITUARIES:
MR. A. TREVE HOLMAN.
DR. LASAR DUNNER.
BOOK REVIEWS
INDEX TO VOLUME 16

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, February 1

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Royal Society of Medicine, 8 p.m., symposium.
GUY'S HOSPITAL: PHYSIOLOGY THEATRE.—5.30 p.m., endocrine demonstration: Aldosterone Metabolism.
LONDON UNIVERSITY.—At Eugenics Theatre, University College, 5.30 p.m., special university lecture by Professor E. Lehmann (California): Efficiency of Non-parametric Tests.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Mr. N. W. Please: Elements of Statistical Methods (V).

Tuesday, February 2

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. Paul Fourman: Magnesium Metabolism in Man.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. J. Hare: Coccal Infections.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Denis Hill: E.E.G. Diagnosis of the Epileptogenic Focus.
LONDON UNIVERSITY.—At Middlesex Hospital Medical School, 5.30 p.m., special university lecture in human anatomy and morphology by Dr. Honor B. Fell, F.R.S.: Experimental Transformation of Cells.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—Milroy Lecture by Dr. L. G. Norman: The Medical Aspects of the Prevention of Road Accidents.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor A. H. C. Ratliff: Fractures of the Femoral Neck in Children.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Lecture Theatre, 5 p.m., Dr. J. G. Dumoulin: Foetal Distress.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. H. C. Grant: Pathology of the Dementias.

Wednesday, February 3

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Rare Tumours of the Skin.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. W. E. Lloyd: Observations on Round Foci.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. A. R. Harrison: Calculi—Metabolic Causes.
●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, 8 p.m., Dr. W. H. Taylor: Metabolic Effects of Trauma.

Thursday, February 4

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor E. B. Verney, F.R.S.: Some Aspects of the Renal Excretion of Water and Electrolytes.
LIVERPOOL MEDICAL INSTITUTION.—5.15 p.m., History of Medicine Lecture by Lord Cohen of Birkenhead.
ROYAL COLLEGE OF PHYSICIANS OF LONDON.—Milroy Lecture by Dr. L. G. Norman: The Medical Aspects of Road Accidents.
ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—At the College, 5.30 p.m., Otolaryngology Lecture by Professor T. Pomfret Kilner: Plastic Surgery of the Upper Jaw.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: posteraduate demonstration in psychiatry.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. Elizabeth Work: Mucopeptides of Bacterial Cell Walls.

Friday, February 5

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. S. Pegum: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners, Mr. G. H. Howells: Cancer of the Larynx.
INSTITUTE OF NEUROLOGY.—4 p.m., Dr. J. Purdon Martin: Observations on Involuntary Movements and Tremor.
LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., special university lecture in pathology by Professor Heinrich Pette (Hamburg): Experimental Demyelinating Diseases and their Implications in Neuro'ogical Diseases of Man.
MEDICAL ELECTRONICS DISCUSSION GROUP.—At Institution of Electrical Engineers, Savoy Place, W.C., 5.30 for 6 p.m., discussion to be opened by Dr. R. A. Buckingham, Ph.D., and Dr. J. M. Tanner: Computers in Medical Use.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., clinical evening. (Cases from 8 p.m.)
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Sir Russell Brock: Some Basic Principles in Cardiac Surgery. (2) 4 p.m., Mr. N. W. Please: Elements of Statistical Methods (VI).
ROYAL INSTITUTION.—9 p.m., Woodhull Lecture by Professor J. F. Danielli, F.R.S.: Some New Approaches to Inheritance and Evolution.
WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Presidential address by Mr. L. H. Savin: Headaches.

Saturday, February 6

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—12 noon, Dr. Roger Maspetiol (Paris): The Factors of Success in Tympanoplasty.
MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., Professor W. Melville Arnott: Management of Cardiac Failure.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—D. A. Alderson, M.B., B.S., D.M.R.D., Part-time Consultant Radiologist (nine half-days weekly) to Stafford Group of Hospitals; M. L. Dyson, M.R.C.S., L.R.C.P., D.M.R.T., D.M.R.D., Part-time Consultant Radiologist (nine half-days weekly) to Wolverhampton and Dudley and Stourbridge Groups of Hospitals; R. G. F. Parker, M.D., D.P.H., Whole-time Consultant Pathologist to Birmingham (Selly Oak) and Birmingham (Sanatoria) Groups of Hospitals; W. Brooks, M.B., B.S., F.F.A. R.C.S., Part-time Consultant Anaesthetist (nine half-days weekly) to Hereford Group of Hospitals.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—M. H. Gough, M.B., B.S., F.R.C.S., Surgical Out-patient Assistant.

LIVERPOOL REGIONAL HOSPITAL BOARD.—D. H. Jones, M.R.C.S., L.R.C.P., D.P.M., Whole-time Consultant Psychiatrist and Medical Superintendent of Deva Hospital, Chester; F. H. Corbitt, M.R.C.S., L.R.C.P., D.P.M., Whole-time Psychiatrist in Mental Deficiency at Greaves Hall Hospital, Banks, near Southport.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—W. B. Harman, L.M.S.S.A., Assistant Physician (S.H.M.O.), Geriatric Department, Hendon Group Geriatric Service; S. Mattingly, M.B., B.S., M.R.C.P., D.Phys.Med., Consultant in Physical Medicine, Garston Manor Medical Rehabilitation Centre; W. M. O. Purcell, M.D., M.R.C.P., M.R.C.P.I., D.M.R.D., Consultant Radiologist, Whittington and New End Hospitals; R. E. Eban, M.B., B.Chir., F.F.R., M.R.C.P., Consultant Radiologist, King Edward Memorial Hospital, Ealing, Queen Victoria Hospital, Hanwell, and South Middlesex Hospital, Isleworth.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Beadles.—On January 4, 1960, in a nursing-home, Bournemouth, Hants, Hugh Stanley Beadles, M.R.C.S., L.R.C.P., of Ladymead, Wareham, Dorset, formerly of Reading, Berks, aged 84.
Draper.—On November 26, 1959, at Gray Gables, 230, Leicester Road, Narborough, Leicester, Thomas Draper, F.R.C.P.Ed.
Earlam.—On January 1, 1960, at Quendale, North Mossley Hill Road, Liverpool, Lancs, Francis Earlam, M.D., aged 58.
Greaves.—On November 11, 1959, at Sheffield, Robert Handley Greaves, M.B., Ch.B., aged 63.
Harries.—On January 12, 1960, at University College Hospital, Eric Henry Rhys Harries, M.D., F.R.C.P., D.P.H., aged 78.
Jamieson.—On January 5, 1960, in hospital, Harold George Rannie Jamieson, M.B., Ch.B., of 61, Adeyfield Road, Hemel Hempstead, Herts, formerly of 1, High Street, Manchester, aged 72.
Madill.—On January 5, 1960, in hospital, Edinburgh, Joseph Thomas Herbert Madill, M.B., Ch.B., F.R.F.P.S., D.P.M.
Parsons.—On January 4, 1960, Laurance Dudley Parsons, M.B., Ch.B., D.T.M., formerly of Gibraltar, and Colombo, Ceylon, aged 86.
Readman.—On January 3, 1960, in a nursing-home, Whitby, Yorks, Thomas Readman, L.R.C.P.&S.Ed., L.R.F.P.S., of Beverley, Yorks, aged 97.
Shaw.—On January 6, 1960, Thomas David Stuart Shaw, M.B., C.M., of Rosebank, Castle Douglas, Kirkcudbrightshire, formerly of Lichfield, Staffs.
Smith.—On January 3, 1960, Helen Evelyn Smith (formerly Rogerson), M.D., D.P.H., D.P.M., of 166, Evington Lane, Leicester.
Tanton.—On January 7, 1960, at St. Leonards-on-Sea, Sussex, Edgar Tanton, F.R.C.S.
Wedd.—On January 7, 1960, Gilbert Wedd, M.B., B.Ch., of Sandy Nap, Crescent Road, Wellington, Salop.
Wood.—Percival Wood, M.R.C.S., L.R.C.P., of 3, Britten House, Chelsea, London, S.W.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Prognosis in Rhesus Incompatibility

Q.—*A patient is B Rh-negative; her husband is homozygous O Rh-positive. The first child—6½ lb. (2.9 kg.), no antibodies—was unaffected, but the second—5½ lb. (2.5 kg.), three weeks premature, antibodies 1 : 16, no saline—needed two replacement transfusions. The second baby's Hb at birth was 110%. Would this baby be considered seriously affected? What would be the risks and chance of survival of a third child?*

A.—From the information given it would appear that the second baby was moderately affected. Since exchange transfusion was performed in the presence of a haemoglobin level of 110% it must be presumed that the serum bilirubin level was elevated. This, however, is not necessarily a matter of serious import for the future, because, by prompt and adequate treatment after birth, it is technically possible to keep a baby's bilirubin level below that which will cause kernicterus. A third child would almost certainly be affected by haemolytic disease, but it is impossible on the history to predict how severely. It is now recognized that there is "a strong tendency for the severity of erythroblastosis to be quite similar in the same family."[1] This means that, contrary to earlier views, the disease pattern is not necessarily progressive and a sequence of babies may be all equally affected. In the event of another pregnancy, a valuable guide to the intensity of the foetal reaction might be obtained by studying the maternal antibody titre by a method such as the indirect antiglobulin technique described by Tovey and Valaes.[2] Such an investigation might actually improve the prospects for the child by indicating the optimum time for its delivery.

There has been a tendency to take too gloomy a view of the situation of a woman sensitized to the rhesus factor. In general it can be stated that, unless such a woman has had, despite a properly managed pregnancy and labour, a child born dead as a result of iso-immunization, the prognosis for her next child is quite good. This assumes that she receives all modern care and treatment. An excellent survey of the problem of rhesus incompatibility is given in the monograph by Allen and Diamond.[1]

REFERENCES

[1] Allen, F. H., and Diamond, L. K., *Erythroblastosis Foetalis*, 1958. Churchill, London.

[2] Tovey, G. H., and Valaes, T., *Lancet*, 1959, **2**, 521.

Chapped Hands

Q.—*What may be done to prevent chapping and soreness of the hands due to frequent washing?*

A.—Soap solution is a primary irritant of the skin—that is to say, it will damage the skin of any normal person if it is supplied in sufficient concentration and for a sufficient length of time. The chapping and soreness of the hands which follows excessive washing is a mild degree of dermatitis which may be partly due to water but is chiefly due to the action of soap. Most, if not all, other cleansers have a similar effect.

The only real answer to this question is, therefore, that the frequency and duration of washing should be reduced when these symptoms appear. If this is not practicable several different remedies may be sought. Firstly, a trial may be made of different soaps and soapless cleansers. Second, exposure of the hands in domestic work can be cut down by the provision of a washing-machine and similar devices. Third, the use of rubber gloves may be helpful, particularly if a cotton glove is worn inside. It is of course a general experience that if rubber gloves are worn for substantial periods the skin beneath becomes macerated and may suffer accordingly. Fourth, barrier creams are often recommended, but the protection they afford is doubtful. Water-resistant barrier creams usually contain oils and/or silicones and are intended to form a layer which soap and water does not penetrate. Although this seems right in principle, the fact remains that barrier creams have never caught on with housewives although they have been tried a good deal. A layer of lanoline applied to the skin before doing wet jobs is probably just as effective. Finally, the application of grease and glycerin to the skin after washing will help to counteract the effects of soap and water.

Bulbar Palsy

Q.—*Have there been any recent advances in the treatment of bulbar palsy?*

A.—The term bulbar palsy means weakness or paralysis of the muscles supplied by the cranial nerves with motor nuclei in the medulla, and there are a number of different pathological processes which may cause it. The treatment of acute bulbar palsy, occurring in such conditions as anterior poliomyelitis, brain-stem encephalitis, or vascular lesions involving the pons and medulla, has improved considerably with the recognition of the importance of postural drainage and by the introduction of positive pressure respiration combined, if necessary, with a tracheotomy. Similar methods, combined with an intravenous drip containing neostigmine, may be life-saving in the acute bulbar palsy of myasthenia gravis. It is possible, however, that the question refers particularly to the chronic bulbar palsy of motor neurone disease, and there have, unfortunately, been no recent advances in the treatment of this condition.

Blepharitis

Q.—*What is the present treatment for blepharitis?*

A.—Blepharitis most commonly arises from neglected conjunctivitis, when mucopurulent discharge dries into crusts which cling to the eyelashes and eyelid margins. Repeated contamination by fingers, especially in children, prolongs and aggravates the trouble. In such patients the prime need is removal of all crusts. If these crusts are too firmly adherent to be discharged by cotton-wool soaked in warm water they should first be softened with hydrogen peroxide. Painting of the eyelids with tinctorium (a solution of crystal violet and brilliant green) twice a day for several days, preceded on each occasion by removal of any further crusts that may have formed, is usually effective in this form of blepharitis, unless the patient persists in reinfecting himself.

Less commonly we find blepharitis linked with facial seborrhoea and a greasy scalp. If so, a spirit lotion for the scalp, together with appropriate ointment for the skin of the face, indirectly helps to clear the eyelids.

Thirdly we must keep in mind the possibility of allergic irritation. Cosmetics, rubber eyelash-curlers, the leaves of certain plants, are among the many things that may produce intense blepharitis. The essential treatment for allergic blepharitis is elimination of the noxious influence.

Idiosyncrasy to Quinine

Q.—*A patient has a severe reaction after taking even the smallest amount of quinine in tonic water. A warning symptom of throbbing in the head is followed in two hours by violent muscular cramps in legs, arms, back, and neck, and sometimes by brief unconsciousness. So far she has not suffered from amblyopia. Is there an antidote she could take?*

A.—This appears to be an instance of true idiosyncrasy to quinine. The incidence of reactions of this type is low, but, since quinine is a widely used substance, patients who have experienced alarming symptoms of this nature are not very uncommon. Disturbance of vision does not usually

occur unless a large dose of quinine is taken. There is no drug which will prevent the onset of the reaction. Nicotinic acid has been recommended as an antidote mainly to prevent the visual impairment, but there is little evidence that it is effective. Suitable substitutes, which are equally effective, are now available for most of the medicinal uses of quinine. In the particular case quoted, clearly the solution to the patient's problem is that she should avoid tonic water and use some other diluent in her cocktails.

1314 T.H.

Q.—*Has α-ethyl-isonicotinic acid thioamide (1314 T.H.) been tried out in this country for pulmonary tuberculosis? If so, with what results? Could it be used in cases resistant to streptomycin, P.A.S., and isoniazid? Is the drug available in this country?*

A.—A preliminary report on the use of this drug in Great Britain was published in the *Journal*.[1] This suggested that 1314 T.H. was an effective anti-tuberculous drug. Further trials of it are at present being carried out in this country by the Clinical Trials Committee of the British Tuberculosis Association. The main disadvantage of the drug is that it causes gastrointestinal upset which, in doses of 1 g. daily, occurs in a relatively high proportion of patients. Resistance to the drug develops readily. The present problem is to find what other drug would prevent this resistance emerging. In a patient whose organisms are already resistant to streptomycin, P.A.S., and isoniazid, the use of 1314 T.H. alone is unlikely to give more than temporary benefit, and once the patient's tubercle bacilli have become resistant to the new drug they may well remain so permanently. It is much wiser not to use the drug at present in such a patient but to wait until the current investigations have determined which other of the newer drugs is best to combine with it. 1314 T.H. is not at present commercially available in this country except for research purposes.

REFERENCE

1 Somner, A. R., Ross, J. D., MacLeod, H. M., Stewart, S. M., Horne, N. W., and Crofton, J. W., *Brit. med. J.*, 1959, **1**, 486.

Phosphaturia

Q.—*What treatment would you advise for a man aged 25 suffering from severe phosphaturia and dysuria?*

A.—Many young people become alarmed when they pass cloudy urine, and this consciousness of phosphaturia, which is usually symptomless, is not uncommon in anxious or frankly neurotic subjects. A carefully taken history, and thorough physical examination followed by reassurance that this is a normal phenomenon, are usually sufficient to allay their fears, and no treatment is indicated for what is a physiological phenomenon.

Phosphaturia readily occurs after a heavy protein meal or the excessive intake of milk and alkalis. It is also common after lack of sleep. If the patient is really suffering from dysuria, and the condition cannot be relieved by mild psychotherapy, one of two methods can be used to stop the phosphaturia. The oral administration of aluminium hydroxide will precipitate phosphate as insoluble aluminium phosphate in the intestine and prevent its absorption. Alternatively, the precipitation of phosphates in the urine can be prevented by acidifying the urine with ammonium chloride given orally.

Parham's Bands

Q.—*Are Parham's bands now used for fractures of shafts of long bones? Are they considered satisfactory, and can they be removed after union?*

A.—Parham's bands are now very rarely used. The wide band sometimes led to avascular necrosis of the underlying bone. Also it was felt that an encircling band did not give such satisfactory fixation as a plate and screws. On the Continent, however, it is still very common for encircling wires to be used. If a Parham's band is used, it can, of course, be removed subsequently.

NOTES AND COMMENTS

Hazards of Ice-cream Trade.—Dr. C. D. CALNAN (London, W.C.2) writes: I note that in your answer to the question "What are the special occupational diseases and hazards of the ice-cream trade?" ("Any Questions?" December 5, p. 1271) you have not mentioned the hazards associated with calcium chloride.[1] A number of ice-cream factories use this in a 25% solution as a freezing agent. Contact with the skin is apt to produce "brine boils" similar to those produced by hypertonic saline.

REFERENCE

1 Horsley-Smith, Anne D., *J. industr. Nurses*, 1958, **10**, 76.

P.A.S. in Urine.—Dr. D. N. BARON (London, W.C.1) writes: Your expert has not mentioned two additional abnormal findings in the urine of patients receiving P.A.S. ("Any Questions?" December 12, p. 1352). Some of the drug may be excreted as a glucuronide in sufficient concentration to reduce Benedict's solution (or "clinitest"): reduction equivalent to 1% glucose can sometimes be present, but enzyme tests are negative. On adding Ehrlich's reagent (2% *p*-dimethylaminobenzaldehyde in 50% HCl) to the urine, as in testing for urobilinogen, a yellow colour or a yellowish-orange flocculent precipitate appears—depending on the quantity of P.A.S. excreted. These abnormalities have been known for many years and provided diagnostic problems during the early days of P.A.S. therapy.

OUR EXPERT replies: I feel that Dr. Baron's remarks, though interesting, are not strictly relevant to the question, which was not, after all, "What are the abnormal findings in the urine of patients receiving P.A.S.?" With this reservation, I agree entirely with his remarks.

Battery-operated Photoelectric Haemoglobinometer.—Dr. I. KENNEDY (Eku, Nigeria) writes: As interns in Capetown in 1953, my fellow housemen and I used the American battery-operated Spencer haemoglobinometer. It is a small instrument operated by two torch batteries and can be easily carried in the hand. Checked against the M.R.C. machine, it is accurate enough for routine ward use and is graduated in grammes and Sahli and Haldane percentages. For mission use it is very satisfactory, and at our hospital we do not now saponize the blood before readings as we have found it saves time, and anaemias here are so gross that the gramme or so difference is not important. Most readings are done by African technicians. The cost in 1953 in South Africa was £20. It must be higher now. It is supplied by the American Optical Co., New York.

OUR EXPERT replies: There are very few simple haemoglobinometers which are of much value, but I should like to point out that the M.R.C. instrument is calibrated by the National Physical Laboratory, and requires no calibration by the user. I do not know how reliable the Spencer is, or how it is calibrated. If the instrument can be checked against one of the standard haemoglobinometers I should think it would be extremely useful.

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